Diet, dietary supplements and dietary change in cancer survivors and cancer-free persons – the Norwegian Women and Cancer study and the European Prospective Investigation into Cancer and Nutrition

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Abstract

This thesis focuses on diet and dietary change in women who have breast or colorectal cancer, compared to cancer-free women in the Norwegian Women and Cancer study (NOWAC; Kvinner og kreft). The use of dietary supplements in the European Prospective Investigation into Cancer and Nutrition (EPIC) is also described. Finally, the association between use of cod liver oil and other supplements and survival among patients with solid tumours from the NOWAC-study is presented.

Cross-sectional results from the NOWAC-study showed that the differences in diet among women with breast cancer (n=666) and healthy women (n=54 314) were not very large, but women with breast cancer ate more fruits and vegetables. Particularly women who had answered the questionnaire less than five years after diagnosis differed from healthy women. There was also a lower level of physical activity and more dietary supplement users among these women.

Change in diet among women who got colorectal (n=130) or breast cancer (n=563) compared to changes among cancer-free women (n=43 154) was evaluated in a follow-up study over almost six years. Those who got breast cancer increased fruits and vegetables intake more than cancer-free women did. Milk intake was unchanged among those who got colorectal cancer, and decreased among cancer-free women. Body mass index and alcohol consumption increased similarly in all groups. Smoking cessation was more common among cancer survivors. Women with breast cancer answering the questionnaire more than 2.4 years after diagnosis reported larger changes than those answering closer to diagnosis. Women diagnosed in stage 2 reported larger changes than women diagnosed in stage 1.

The comparison of dietary supplement use in the EPIC-study (n=36 034) revealed a clear North-South gradient, with almost ten times as many female users in Denmark as in Greece. The difference was even larger among men. Among Norwegian women 61.8% were users, compared to 67.0% among Danish women. Vitamins, minerals and combinations of them were most commonly taken in most countries. Cod liver oil and other oil-based supplements were common particularly in Norway and the UK.

Within the NOWAC-study we studied survival rates among those who developed solid cancers (n=2 997) in relation to use of cod liver oil and other dietary supplements before diagnosis. Whole-year users of cod liver oil and of other dietary supplements had increased survival, particularly lung cancer patients. Occasional use of other supplements also increased survival. The effect persisted even after adjustment for age, stage and smoking. Some of the effect might be a result of factors we could not adjust for. More research is needed in order to clarify the association.

Samandrag

Avhandlinga dreiar seg om kosthald, kosttilskot og endringar i kosthald hos kvinner som har bryst- eller tarmkreft, jamført med kreftfrie kvinner i Kvinner og kreft-studien. I tillegg skildrar ho bruken av kosttilskot i European Prospecitve Investigation into Cancer and nutrition (EPIC). Til slutt blir assosiasjonen mellom bruk av tran og andre kosttilskot og overleving blant pasientar med kreftsvulstar frå Kvinner og kreft presentert.

Tverrsnittsstudien frå Kvinner og kreft viste at skilnadene i kosthaldet til kvinner som hadde brystkreft (n=666) og friske kvinner (n=54 314) ikkje var så store, men kvinner med brystkreft åt meir frukt og grønsaker. Det var særleg kvinner som hadde fylt ut spørjeskjemaet mindre enn fem år etter diagnosen som skilde seg frå friske kvinner. Det var også eit lågare nivå av fysisk aktivitet og fleire brukarar av kosttilskot blant desse kvinnene.

Oppfølgjingsstudien såg på om kosthaldet endra seg blant kvinner som fekk tarmkreft (n=130) eller brystkreft (n=563) jamført med kreftfrie kvinner (n=43 154). Dei som fekk brystkreft auka inntaket av frukt og grønsaker meir enn kreftfrie kvinner. Mjølkeforbruket var uendra blant dei som fekk tarmkreft, og minska blant kreftfrie kvinner. Auken i kroppsmasseindeks og alkoholforbruk var lik mellom gruppene. Røykeslutt var vanlegare blant dei som fekk kreft. Kvinner med brystkreft rapporterte større endringar om dei svara på siste spørjeskjema meir enn 2.4 år etter diagnosen enn før dette tidspunktet. Dei som fekk brystkreftdiagnosen i stadium 2 gjorde større endringar enn dei som fekk diagnosen i stadium 1.

Samanlikninga av kosttilskotsbruken i EPIC-studien (n=36 034) synte ein tydeleg nord-sør gradient, med nesten ti gonger så mange kvinnelege brukarar i Danmark som i Hellas. Blant menn var skilnaden endå større. Det var 61.8% brukarar blant norske kvinner, mot 67.0% blant danske kvinner. Vitaminar, mineral og preparat med både vitaminar og mineralar var vanlegast i dei fleste landa. Særleg i Noreg og Storbritannia var også tran og andre oljebaserte kosttilskot vanleg.

Innanfor Kvinner og kreft-studien såg vi på overlevingsratane blant dei som fekk kreftsvulstar (n=2 997) i høve til om dei hadde teke tran eller andre kosttilskot før diagnosen. Dei som brukte tran eller andre tilskot heile året hadde noko auka overleving, særleg dei som fekk lungekreft. For andre kosttilskot såg ein også effekt av bruk 1-6 gonger i veka. Effekten var der sjølv etter justering for alder, stadium og røyking. Noko av effekten kan ha kome av faktorar vi ikkje kunne justera for. Meir forsking trengst for å underbyggja resultata.

List of papers

The thesis is based on the following papers, referred to in the text as papers 1, 2, 3 and 4.

1. Diet among breast cancer survivors and healthy women. The Norwegian Women and Cancer study. *Eur J Clin Nutr 2006, 60(9):1046-54.*

2. Dietary change among breast and colorectal cancer survivors, and cancer free-women in the Norwegian Women and Cancer cohort study. *In manuscript.*

3. Use of dietary supplements in the European Prospective Investigation into Cancer and nutrition calibration study. *In press, Eur J Clin Nutr (Supplement) 2009.*

4. Cod liver oil, other dietary supplements and survival among cancer patients with solid tumours. *Int J Cancer 2009, Sep 1;125(5):1155-60.*

Abbreviations

24-HDR= 24-hour dietary recall

BMI= body mass index

CAM= complementary and alternative medicine

CI= confidence interval

EPIC= European Prospective Investigation into Cancer and Nutrition

FFQ= Food Frequency Questionnaire

HR= hazard ratio

NOWAC= Norwegian Women and Cancer study

RR= relative risk

SENECA= Survey in Europe on Nutrition and the Elderly; a Concerted Action

WCRF/AICR= World Cancer Research Fund/American Institute of Cancer Research

WINS= Women's Intervention Nutrition study

WHEL= Women's Healthy Eating and Lifestyle study

1 Introduction

The total number of persons diagnosed with cancer and alive in the world in 2008 was estimated to be 25 million, and by 2030 it is expected to be 75 million persons alive with cancer within five years of diagnosis [1]. Cancer is today the most important cause of years of lives lost in Norway [2]. Even though many die from cancer in the end, in recent years treatment and prevention of cancer have improved, and with technology and programs for early detection of cancer more available, more and more people are living with cancer, and this number will continue to increase [3]. For example, the five-year survival rate for breast cancer was 85.6% among those diagnosed between 1997 and 2001 [4]. This is an increase of 35.2% compared with those diagnosed in 1957-61, the first period covered by the Cancer registry of Norway. For all cancer sites taken together, the chance of surviving cancer is now 53.8% higher for women than it was in the first period of the registry, and 62.2% of those diagnosed with cancer live more than five years after their diagnosis [4].

The most frequent cancers in women in Norway are breast cancer with 75.6 cases per 100 000 person-years, colorectal cancer (including cancers in rectosigmoid junction and anus) with 34.6 cases per 100 000 person-years and cancer in the lung and trachea with 23.0 cases per 100 000 person-years in the period 2003-2007 [5]. By the end of 2007, over 183 252 men and women who had ever been diagnosed with cancer were alive in Norway. Among them 33 889 had experienced breast cancer as their first primary cancer, 24 937 colorectal cancer and 4 536 lung cancer [5].

In Europe it was estimated that 7 281 590 persons were living with a prevalent cancer within five years of diagnosis in 2002 [6]. Among women the most common incident cancers were those of the breast, colorectum and lung, among men the most common incident cancers were those of the lung, prostate and colorectum.

1.1 Cancer survivors

Cancer survivorship was first described as a concept in 1985, by Fitzhugh Mullan, a medical doctor diagnosed with cancer [7]. The National Cancer Institute in USA has adapted their definition from the National Coalition for Cancer Survivorship: “An individual is considered a cancer survivor from the time of the diagnosis, through the balance of his or her life. Family members, friends and caregivers are also impacted by the survivorship experience, and are therefore included in this definition” [8]. Including family, friends and caregivers in the definition is somewhat controversial, even though a cancer diagnosis will have an impact not only on the person who gets it, but also on persons in her/his surroundings. The

recently established "Journal of Cancer Survivorship" recognizes that cancer also affects family and caregivers, but chose not to include them in the definition used for the journal, in order to keep focus on the research on survivors, which still is an emerging field of research [9]. The term cancer survivor/cancer survivorship is not as much used in Europe and European literature as in the US. In this thesis, the term cancer survivor is confined to persons who have ever had a cancer diagnosis.

The new definition, labelling patients as cancer survivors from the date of diagnosis, as opposed to when they had been disease-free for five years, have had effect both on how the disease has been perceived and the treatment options given to patients [10]. Both technological and other developments have contributed to transforming cancer from almost incurable to a disease that some will be cured for, and many will live long with. Consequently, it is important to prompt patients and clinicians to think early about long-term effects. For example, the improved survival for childhood cancers has made treatment regimens that can preserve fertility an issue, and as cancer survivors are at increased risk of second cancers and other diseases, promoting healthy lifestyles in survivors has become a priority [11] (see 1.1.1 and 1.1.2).

Cancer survivorship encompass several phases and people with very differing needs, but at least three periods are often distinguished: the period after diagnosis, but before treatment, the treatment period, and the period after treatment [12]. The period after treatment will differ depending on whether the treatment was successful or unsuccessful, whether the patient develops a metastasis or a cancer at a different site or not. The definition of cancer survivorship research used by the US National Cancer Institute is presented in box 1.

Box 1: Cancer survivorship research

Cancer survivorship research encompasses the physical, psychosocial, and economic sequelae of cancer diagnosis and its treatment among both paediatric and adult survivors of cancer. It also includes within its domain, issues related to health care delivery, access, and follow up care, as they relate to survivors. Survivorship research focuses on the health and life of a person with a history of cancer beyond the acute diagnosis and treatment phase. It seeks to both prevent and control adverse cancer diagnosis and treatment-related outcomes such as late effects of treatment, second cancers, and poor quality of life, to provide a knowledge base regarding optimal follow-up care and surveillance of cancers, and to optimize health after cancer treatment.

Office of Cancer Survivorship, National Cancer Institute [8]

1.1.1 Health issues for cancer survivors

Even when the cancer is cured, cancer survivors are facing a diversity of sequelae including physical and physiologic problems that may require medical treatment, as well as societal and interpersonal issues and fear of recurrence [3].

The risk of developing second cancers in survivors are higher than the risk of developing primary cancers in the general population, and in the US cancer survivors represent 3.5% of the population, but account for about 16% of the incident cancers [13]. Cancer survivors are also at higher risk of other conditions such as cardiovascular disease, diabetes, and osteoporosis compared with age-matched controls [13-15]. US data show that cancer patients are significantly more likely to die from non-cancer causes than the general population [14]. This may result from side effects of the cancer treatment, genetic predisposition and that common lifestyle factors are parts of the causes for all these conditions. A problem with studies on treatment related late effects/long-term effects is that the results we get today originate from treatment regimens that may now be obsolete. Still, the information about adverse effects of older therapies can help improve the new therapies, and the design of surveillance programs.

In Norway, cancer survivorship research is rather limited. Much of the research on treatment effects has been done on testicular cancer survivors, e.g. [16]. A population based study showed that survivors of six different cancers diagnosed five years or more prior to the study reported poorer health than their age- and gender-matched controls did [17]. The survivors had used both general practitioners (70% vs. 66%) and the specialist health care system (43% vs. 28%) more often than the controls the last 12 months preceding the survey. In addition, the proportion of survivors on social welfare benefits was higher than in the controls (14% vs. 11%). Seventy percent of the survivors reported at least one health complaint, compared to 66% of the controls. There were no differences in smoking, obesity and inactivity [17].

1.1.2 Dietary issues for cancer survivors

Getting adequate amounts of foods and nutrients could be a challenge for cancer survivors. Nutrients could be supplied from foods, but also from dietary supplements. The dietary issues for cancer survivors differ according to the phase of survivorship. For some cancer sites (e.g. lung cancer) and for cancers detected in an advanced stage the general condition of the patient is often quite poor [18,19]. This means that the cancer patient may enter the treatment with compromised nutritional status. A study from the UK found that 28% of the lung cancer patients had poor nutritional status defined as low pre-

operative albumin, recent history of weight loss or low BMI [18]. Nutritional status had no impact on hospital mortality, and cardiac or respiratory complications. However, nutritional status was a predictor for long term survival, independently of tumour extension and staging.

Depending on the treatment chosen for each patient, the treatment itself can affect the nutrition status and appetite. Examples of nutrition-related side-effects of treatment are anorexia, early satiety, changes in taste and smell, disturbances of the gastrointestinal tract, nausea, vomiting, weight change, cachexia, loss of lean mass and sarcopenia [19]. If any of these symptoms occur, normal food choices and eating patterns may need to be temporarily adjusted to optimize intake and meet nutritional needs. A Norwegian study of dietary intake and nutritional indicators during radiotherapy for rectal cancer showed a transient reduction in energy intake and nutritional indicators, but no change in nutritional quality [20]. When active cancer treatment is ongoing, the overall goals for nutritional care for survivors should be to prevent or reverse nutritional deficiencies, to preserve lean mass, to minimize nutrition-related side-effects, and to maximize quality of life [19]. For those at risk of unintentional weight-loss, preventing weight loss and maintaining energy balance is an additional goal. Some people chose not to utilize conventional therapy, or use complementary therapies such as radical diets, energy restriction, orthomolecular nutrition or specific diet to cure the disease [12].

For most survivors, cancer treatment occupies a limited time period, and the diet after treatment is of more concern. Some forms of treatment damage the metabolic function; this particularly concerns patients where parts of the digestive tract (mouth, oesophagus, stomach, small intestine or colon) have been removed or irradiated so that absorption is decreased. The specific challenges of this group will not be dealt with in this thesis.

1.1.2.1 Prevalence of dietary and lifestyle factors in cancer survivors

Studies relating food and nutrition to cancer have focused mostly on aetiology and primary prevention [21]. Studies of populations after cancer diagnosis have focused largely on therapeutics or prognostic factors, and much less on lifestyle factors. To the extent that lifestyle factors have been studied in relation to prognosis, it has been the impact on quality of life, not survival or recurrence that has dominated the literature. The diet one observes among cancer survivors might be a result of pre-diagnosis dietary habits that have been continued, or also of dietary changes triggered by the diagnosis. Diet and other lifestyle habits are known to influence cancer risk [12], so unless there has been change

from pre-diagnosis habits, survivors, at least from some cancers, could be expected to behave less in agreement with recommendations than the cancer-free population.

Comparisons of lifestyle factors in cancer survivors with age-matched controls or scientific recommendations have often yielded discouraging results [22-27]. Only a minority meet the five-a-day recommendation for fruit and vegetables in survivor cohorts [23,24,26], and studies comparing survivors to non-cancer controls found no differences in fruit and vegetable intake [25,27]. Considering fat intake, the results have varied: one survivor study showed a high prevalence of low-fat diets (69%) [26], another found fat intakes similar to the general population [24], while a study with a non-cancer control group showed a low prevalence of low-fat diets in both groups [25]. Fibre intake was low [24], and not different from the control group [25]. One study reported high prevalence of overweight, and higher weight gain in younger breast cancer survivors than older [24]. Similar prevalence of overweight and risky drinking behaviours between survivors and controls has been reported [25,27]. Similar alcohol consumption was also reported from another study with non-cancer controls [22]. Except for one Australian study, all studies were done in US populations, so how these results reflect the Norwegian or European situation is not known.

Although one study reported that most survivors engaged routinely in physical activity [26], only a minority met the goal of 150 minutes of moderate to strenuous or 60 minutes of strenuous activity per week [22,23,25]. Two studies reported that the levels of physical activity were similar between survivors and controls [25,27], while another reported that survivors were 9% more likely to meet physical activity recommendations [22]. Few differences in smoking habits have been found, except a tendency of more smoking among younger survivors than controls [22,25]. An Australian study found that survivors, particularly those under 40 years were significantly more likely to be current smokers [27]. In the studies of survivors only, the prevalence of smoking were ten percent or less [23,24,26].

The differences in results between studies could be real, but also an effect of methodological differences (only one study used a full dietary registration [24]) or differences in study population characteristics and cancer sites studied.

Patients with pre-invasive lesions, e.g. adenomas, are an intermediary group between cancer-free and cancer survivors. A prospective Norwegian study found weak inverse associations between adenoma growth and intake of fruit and berries, carbohydrates, and between adenoma recurrence and vegetable intake [28].

1.1.2.2 Dietary and lifestyle change in cancer survivors

A number of reports have suggested that cancer survivors adopt diet and lifestyle changes in hope of achieving improved health, often without advice from health professionals [29-38]. Most frequently the changes take a healthy direction, cutting down on fat consumption and increasing the intake of fruits and vegetables [39]. However, most of the studies on cancer survivors have been done in US populations, have a retrospective or cross-sectional design, have not used validated methods for measuring diet or have not had a comparison group of cancer-free persons.

How dietary change (and other lifestyle change) in cancer patients is associated with time is not well described, neither whether it is persistent, nor if it differs according to time since diagnosis [3,39,40]. Variations in change according to stage of disease are seldom studied [3]. However, as described in 1.1.2.1, health behaviours do not seem to differ much between cancer survivors and healthy populations or non-cancer controls, at least not in a cross-sectional perspective [22,24,25].

Much of the knowledge about cancer survivors and diet/lifestyle has come from studies of breast cancer survivors and studies of childhood cancer survivors. Some recent studies of colorectal cancer survivors show results similar to those found among breast cancer survivors [33,37,41,42]. In a Norwegian intervention study patients with colorectal polyps were given either a mixture of vitamins and minerals or a placebo [43]. One year after the intervention no major dietary changes which could be associated with a changed susceptibility for malignancy were found.

This study and others were reviewed in the 2007 WCRF/AICR expert report [12,44]. Meta-analyses of trials on dietary modifications and supplements used by cancer patients and patients with preinvasive lesions were performed, and 25 trials with cancer patients and 34 with patients with preinvasive lesions were found. Trial quality was generally low, and there was no clear evidence of benefit or harm with any of the exposures, neither on all-cause mortality nor on cancer mortality, disease-free survival, cancer recurrence, second primary cancer, recurrence of a preinvasive lesion or progression to cancer. Additionally, two large, multicentre, randomized trials of dietary modification in breast cancer survivors published after the first literature review [45,46] (see below) were taken into account by the expert panel. The final report stated that no conclusions could be derived from the results of studies on 'healthy diets' for cancer survivors [12]. The panel's advice for cancer survivors was therefore to follow the dietary recommendations for cancer prevention.

Two large US prospective intervention studies have focussed on dietary change in breast cancer survivors. The Women's Intervention Nutrition Study (WINS, n=975 in

intervention, n=1462 in control group) tested the effects of a low-fat diet on breast cancer recurrence risk [45]. Interim results showed a lower risk of recurrence (HR 0.76, 95% CI 0.60-0.98, p-value 0.08), but the intervention group had more extensive surgical procedures and lost weight, which might account for the effect. Women with negative hormone receptor status tumours had a more beneficial effect [45]. The Women's Healthy Eating and Lifestyle (WHEL, n=1537 in intervention, n=1551 in control group) study tested the effect of a diet high in fruits and vegetables and low in fat on breast cancer recurrence [46]. The intervention did not affect prognosis or mortality, neither did it lead to changes in body weight between the intervention group and the control group [46]. Several explanations for the differences in results between these studies have been discussed, including different timing of study entry relative to diagnosis, differences in fat reduction, differences in intervention maintenance, differences in weight reduction and difference in treatments between study groups [47,48]. The definitive results from the WINS study were expected in mid-2008 [48], but have not been published by the end of March 2009.

The WHEL study included women up to 4 years after diagnosis, mean time between diagnosis and randomization was approximately 2 years. The participants reported making dietary changes after diagnosis, before randomization, and particularly changes in fat consumption were more likely with longer time since diagnosis [49]. If there is a critical time window shortly after diagnosis or completion of treatment, it might have been missed. Earlier interventions as in the WINS study, or pre-diagnosis diet might be more important for recurrence. Results from the control arm of the WHEL study suggest that women with higher baseline plasma carotenoid levels had a significantly reduced risk for breast cancer recurrence (HR 0.57, 95% CI 0.37-0.89 for highest compared to lowest quartile of carotenoids) [50]. However, quartile CIs overlapped, so threshold or dose-response patterns could not be addressed. Since carotenoids are considered biomarkers for fruit and vegetable intake, this provides some support for a greater likelihood of recurrence-free survival in breast cancer patients who have had higher intakes of fruits and vegetables. In another study from the WHEL control arm, the combination of being physically active and eating more than five servings of fruits and vegetables a day at baseline almost halved the mortality (HR 0.56, 95% CI 0.31-0.98, p-value 0.04) compared to having low physical activity and eating less than five servings of fruits and vegetables [51]. This effect was seen both in obese and non-obese women. Given these conflicting results, the WRCF/AICR statement – that no conclusions can be drawn seems prudent.

However, these large studies have, if nothing else provided evidence that dietary changes are feasible [52], and even if the results might not directly affect recurrence rates, the risk for other adverse health effects might have decreased. Some see the cancer

diagnosis as a “teachable moment”, a point in time where the motivation for making healthy changes to diet and lifestyle is strong, and an occasion for health care providers to engage not only in curative treatment, but also long-term health promotion [39].

1.2 Dietary supplement use

Dietary supplements are alternative sources of nutrients. Despite this they are not always queried in dietary surveys, so nutrient intakes may be underestimated. There is no commonly agreed definition for dietary supplements, neither for research, surveillance or regulatory purposes [53]. Sometimes dietary supplements are reported with medications, and sometimes they are reported as complementary and alternative medicine (CAM), particularly if taken in large doses. This is one of the reasons why questions and definitions vary so much between studies. The focus of this thesis is dietary data, not CAM information, still CAM data are used to enrich the background data when no other data have been found.

Dietary supplement use is increasing [54], and although Norwegian prospective or repeated studies are lacking, consumption data show that households were spending more than five times more on vitamins, minerals, herbs and other dietary supplements in 2006 compared to in 1988 [55]. Studies show that around 35% of the female adult population take cod liver oil [56-59], and 40-60% use other dietary supplements [56,60]. Cod liver oil use has a long tradition in Norway, and the high content of vitamin D has been important in preventing osteomalacia and rickets during the winter season when there are periods with low or no cutaneous production of vitamin D [56,61,62]. It is also an important source of n-3 fatty acids [63].

The SENECA study of elderly persons compared dietary supplement use in 18 towns in 12 European countries, and is one of few comparative studies in Europe [64,65]. This study showed large geographical differences in dietary supplement use, with higher frequency of use in Northern countries. Norwegian participants reported high frequency of use, 40-50% of the participants took supplements in the 1988/89 survey [65]. Compared to nutrient intake data, the supplement use did not seem to be motivated by low nutrient intakes or poor diet quality [65]. Both at the follow-ups in 1993 and in 1999 23% of the subjects took dietary supplements [64]. Norway did not participate in the follow-up studies. Since dietary supplement use is increasing, these data are now rather old, the questions posed were not very elaborative, the local study samples small and not representative, and the study only included elderly persons (80 years and older at enrolment), more comparative studies of dietary supplement use in Europe are warranted.

A study from the US suggested that 73% of the adult population had taken dietary supplements the previous year [66], other studies have found lower prevalences, but notes methodological differences [67].

Comparing supplement use across studies is difficult due to differences in methods and definitions [53]. What is defined and perceived as supplements may differ between studies and between populations. Likewise, the time frame for supplement use may vary, e.g. the last month or the last year. Also, the level of detail in the supplement information varies, e.g. whether fixed or open questions are used, and whether information on contents and dosage is collected (cfr. section 3.3). This means that it is difficult to compare the level of dietary supplement use in Norway with other countries. Some countries or studies have developed dietary supplement databases [68], and in the US a database of dietary supplements based on analysed products is being developed [69]. No common European supplement database exists. In Norway a database is in progress [59].

Some groups use supplements more often than others, most studies show that female gender, older age, higher socioeconomic status and lower BMI [56,70-76] predict supplement use. Several studies have also shown that supplement use is higher in various patient groups [77-80].

1.2.1 Prevalence of dietary supplement use in cancer survivors

Many studies have measured dietary supplement use in cancer survivors, and particularly breast cancer survivors have been well studied [77]. A recent systematic review from the US suggests that supplement use is widespread in cancer patients and longer-term survivors [77]. In studies where different cancer sites were combined, 64-81% of survivors used any kind of vitamin or mineral supplement, and 26-77% used any kind of multivitamin, compared to the adult US population where ca 50% used dietary supplements and 33% used multivitamin/multimineral supplements. Between 14 and 32% of survivors started using supplements after diagnosis, and use differed with cancer site [77]. Dietary supplement use was most common in breast cancer survivors, and least in prostate cancer survivors, and use was most consistently associated with female gender and higher education.

Patients often don't inform their doctors about their supplement use [77,81]. Given the high prevalence of use, more studies are needed to explore the association between dietary supplement use and cancer treatment toxicity, recurrence, survival, and quality of life. For example, taking antioxidants, particularly in high doses is controversial, as there is concern that they might interfere with radio- or chemotherapy treatments, and thereby reduce survival [19,82]. Some therefore advice patients not to take supplements during treatment [82]. The WCRF/AICR recommendation is to try to meet nutritional needs

through diet alone [12]. The American Cancer Society suggests that during treatment, when it can be difficult to consume a normal diet, a standard multivitamin pill containing up to 100% of the Daily Value could be helpful in covering nutritional requirements [19]. More research is needed before evidence-based clinical guidelines for dietary supplement use among cancer patients and longer-term survivors can be developed [77].

Not many comparative data exist on dietary supplement use among European cancer patients. A European survey found that among 956 patients from 14 countries 35.9% were using CAM, ranging from 14.8 to 73.1% [83]. Herbal medicine and vitamins/minerals were among the most frequently used therapies both after diagnosis and at the time of the study. Subjects reported that they had initiated CAM use after diagnosis, and herbal medicine use had tripled from before diagnosis. Unfortunately, no country specific estimates were given on types of CAM, and the study sample was neither random nor nationally representative, so these data should be interpreted with caution [83].

In Norway, some smaller studies have described dietary supplement use in cancer patients, but with one exception [20] not in relation to dietary intake [84-86]. Among rectal cancer patients surveyed four times from start of therapy till one year after completion, 74% took supplements at some point, but most patients did not use supplements at all registrations [20]. Use was highest one year after completing therapy (71%), and several different types of supplements were taken. Another study surveyed patients (in or after active treatment) attending diagnose specific courses [85]. Among the patients, 56% were using “products from the health food market”, and 36% used such products in relation to their cancer. Younger patients used these products more often than older patients, but no gender differences were found.

Another Norwegian study showed that herbal use among cancer patients receiving palliative or curative chemotherapy treatment did not differ between groups (37% and 38%, respectively) [84]. The study was followed up by an identification and exploration of herb-drug combinations used by cancer patients during chemotherapy [87]. For the 42 patients that used herbs concurrently with chemotherapy, 136 different herb-chemotherapeutic combinations were found. For 48% of the herbal remedies identified no data existed in the literature on possible interactions with chemotherapy.

In a national study comparing cancer patients with poor prognosis (<20% expected five-year survival) and better prognosis (40-60% expected five-year survival) and their use of CAM five years after diagnosis, 18.4% of the poor survival group had used dietary supplements in doses above recommended daily allowances, and 13.4% of the better prognosis group, the difference was not statistically significant [86]. Approximately 7% of

the patients in the two groups reported use of diet as treatment, meaning that they had made radical changes to their diet.

1.2.2 Dietary supplement use, cancer incidence, survival and mortality

Several studies have been performed in order to assess if dietary supplements could reduce cancer risk in the general population or in high risk groups [88]. For well-nourished populations, not much evidence for beneficial effects exists [12,88]. There is convincing evidence that high-dose beta-carotene supplements are a cause of lung cancer in smokers [12]. Recent randomized studies showing no effect of vitamin D and calcium supplementation on colorectal cancer [89], and no effect of selenium and vitamin E supplementation on prostate cancer [90] do not support some of the other conclusions from the WCRF/AICR report.

Even though the trials with dietary supplements for prevention of recurrence and death in cancer survivors reviewed for the WCRF/AICR report generally had more participants and better quality than the dietary intervention trials in cancer survivors, no conclusions about beneficial effects could be drawn [12]. More recently published randomized controlled trials have added to the picture with findings of no effect of alpha-tocopherol and beta-carotene supplementation on upper aerodigestive tract cancer mortality [91], and similarly for vitamins C and E and beta-carotene on cancer mortality [92]. Observational studies have found a possibility for increased risk of fatal prostate cancers in men taking high levels of multivitamins along with other supplements [93]. A Swedish study found no association between use of any dietary supplement or of multivitamins, vitamin C, vitamin E or fish oil specifically and all-cause mortality, cancer or cardiovascular mortality [94]. However, this study noted increased risk of cancer mortality among current smokers using supplements. Similar results were found in the SENECA study, no associations for non-smokers, and increased mortality was observed for smokers using any supplements and vitamin B1 or vitamin B2 supplements.

Few recent studies have looked at dietary supplement use and survival in cancer patients, but a study of nonvitamin, nonmineral supplement use found better survival rates in users than in non-users [95].

2 Aims

The general aim of this thesis was to provide insight into the diet, dietary supplement use and dietary change in cancer survivors compared to a cancer-free control group. Further, to provide descriptive data on dietary supplement use in Europe, and to study the association between use of dietary supplements and survival.

The specific aims were to:

1. Cross-sectionally compare diet and lifestyle in breast cancer survivors and healthy women.
2. Longitudinally describe and compare diet and lifestyle in breast cancer survivors, colorectal cancer survivors and cancer-free women.
3. Describe the use of dietary supplements in ten European countries, and some health-related factors associated with use.
4. Explore the association between use of cod liver oil, other dietary supplements and survival of cancer patients with solid tumours.

3 Material and methods

This thesis utilizes data from two prospective cohort studies, the Norwegian Women and Cancer study (NOWAC) (papers 1, 2 and 4) and the calibration sub-cohort from the European Prospective Investigation into Cancer and nutrition (EPIC) (paper 3). The cohorts are linked, a sub-cohort of the NOWAC study constitutes the Norwegian EPIC study, and the Norwegian part of the EPIC calibration sub-cohort is randomly selected from the Norwegian EPIC study, see figures 3.1 and 3.2.

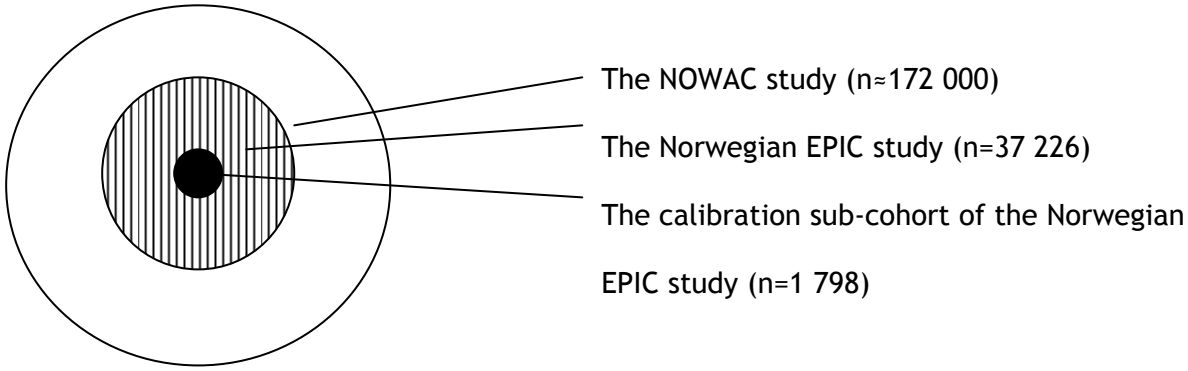


Figure 3.1: Relationship between the NOWAC study and the Norwegian EPIC study. For clarity the sizes of the circles are not proportional to the sample sizes

3.1 The Norwegian Women and Cancer study

The Norwegian Women and Cancer study (NOWAC; Kvinner og kreft) is a national, population-based cohort study which enrolled the first participants in 1991 [96,97]. The primary aim was to investigate the relationship between oral contraceptive use and breast cancer. Due to study logistics, financial reasons and a wish to do methodological substudies, the first enrolment was divided in 24 mailings over seven years (figure 3.2). This thesis only uses data collected from participants included during the first enrolment wave. A second wave of enrolment of new participants started in 2003, and a new recruitment wave is expected to start in the autumn of 2009.

The participants have answered one, two or three questionnaires, and some have participated in one [98] or four 24-hour dietary recalls (24-HDR) [99]. Participants who were born between 1943 and 1957 and agreed to be contacted again have been asked to donate at least one blood sample (figure 3.2).

Questionnaires collected in 1991-1995 only had a limited set of dietary questions, not comparable to those collected from 1996 and onwards. Therefore, the baseline data in this thesis are partly from the NOWAC baseline mailing (1996/97) and partly from the second mailing (1998-99) to those enrolled in 1991/92 (full circle in figure 3.2). Hereafter data collected in 1996-1999 are called thesis baseline in order to distinguish them from the NOWAC baseline data collected in 1991-99. Consequently, the follow-up data in this thesis are partly from the second mailing to those recruited in 1996/97 and partly from the third mailing to those recruited in 1991/92 (dashed circles in figure 3.2). Data collected in 2002-05 are called thesis follow-up, and data collected from 1998 and onwards are called NOWAC follow-up. See appendix II for examples of questionnaires and appendix III for the translation of a questionnaire.

3.1.1 Sampling, invitation and ethical issues

The participants are selected randomly from the Central Person Registry kept by Statistics Norway, using the unique national identity number each inhabitant is assigned by law [100]. The selection is based on year of birth, and some series sampled participants from Northern Norway only. For confidentiality, the national identity numbers are replaced with serial numbers on the material sent to the participants, and in the files the researchers receive.

The selected women receive a letter of invitation together with the questionnaire, a booklet covering most brands of oral contraceptives and postmenopausal hormone therapy sold in Norway, and a pre-paid return envelope. The invitation letter explains the aim of the study, that participation is voluntary and that the participants can withdraw from the study at any time, without giving any reason (see appendix I). One or two written reminders have been sent. The response rate for the first NOWAC mailing was 57% [97]. The process is similar for the NOWAC follow-up mailings; Statistics Norway is given the list of participants who have consented to be contacted again, and sends questionnaires to those alive and residing in Norway. The invitation letter explains why the women are contacted again, that new and updated information is needed, but that participation still is voluntary. The response rate to the second NOWAC mailing was 81% corrected for death and emigration [97]. 80.7% of the invited women who responded to the second mailing also responded to a third mailing (unpublished data).

On all questionnaires the participants were asked to mark that they consent to participate, and the NOWAC study has got a legal exemption from confidentiality rules for medical registries. The study has been approved by the regional committee for medical

ethics, the National Data Inspectorate and the biobanks are managed after directions from the Norwegian Directorate for Health.

3.1.1.1 Study samples

Figure 3.2 (adapted from Lund [97]) gives an overview of the enrolment in the NOWAC-study. Number of women recruited (NOWAC baseline, black boxes), completing second (striped boxes) and third (grey boxes) questionnaires, and number of blood samples are displayed, along with year of enrolment, age and length of questionnaire. For readability, some simplifications have been made regarding length of questionnaire: Series 11-16; 19-24 had 2-8 pages. Series 25 and 27 had four pages; series 26, 28 and 29 had 8 pages. Further, series 29 was collected in 1999, and not in 1998 as depicted in the figure.

As explained above, some of the participants (series 1-13 in figure 3.2) had only a limited set of dietary questions in their NOWAC baseline questionnaire, which could not be used for nutrient calculations. Most of these series were methodological studies testing various questionnaire lengths and other factors that could influence participation rates (series 4-8 and 11-16). To increase the sample size and statistical power, data from questionnaires collected in the same time period (1996-99), with similar content were pooled together (series 14-16, 19, 20, 22, 23, 26, 28 and 29) to form the thesis baseline (within the full circle in figure 3.2). The series in dashed circles (except 34), are the thesis follow-up series. The thesis follow-up series all had participants both from series with no or limited dietary questions in addition to those with comprehensive dietary questions. Only participants with comprehensive dietary registration at thesis baseline were included in the analyses. Figure 3.3 focuses exclusively on the series included in the thesis.

A small sub-sample of women drawn from a young age-band (aged 40-44, series 21, n=586), was not included in paper 1, and therefore also not in paper 2 which is a follow-up study of paper 1, but contributed cases for paper 4.

Series 28 and 29 constitute the Norwegian EPIC cohort, and the participants in the calibration study (paper 3) were drawn randomly from these series. The EPIC calibration study participants who also filled in the thesis follow-up questionnaire (series 39 and 42) and developed cancer after completing the thesis baseline questionnaire (series 28 and 29) were eligible for all four papers.

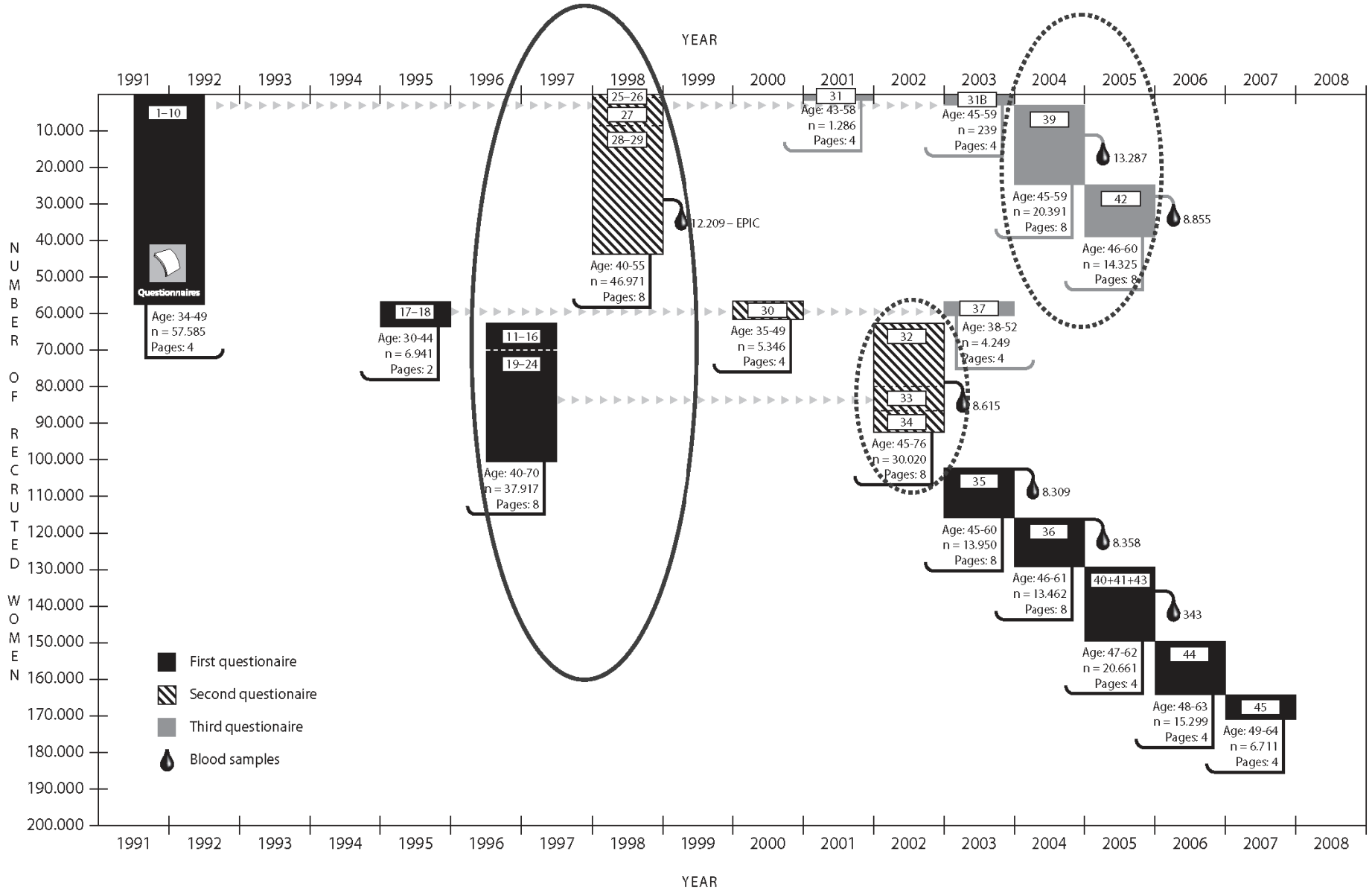
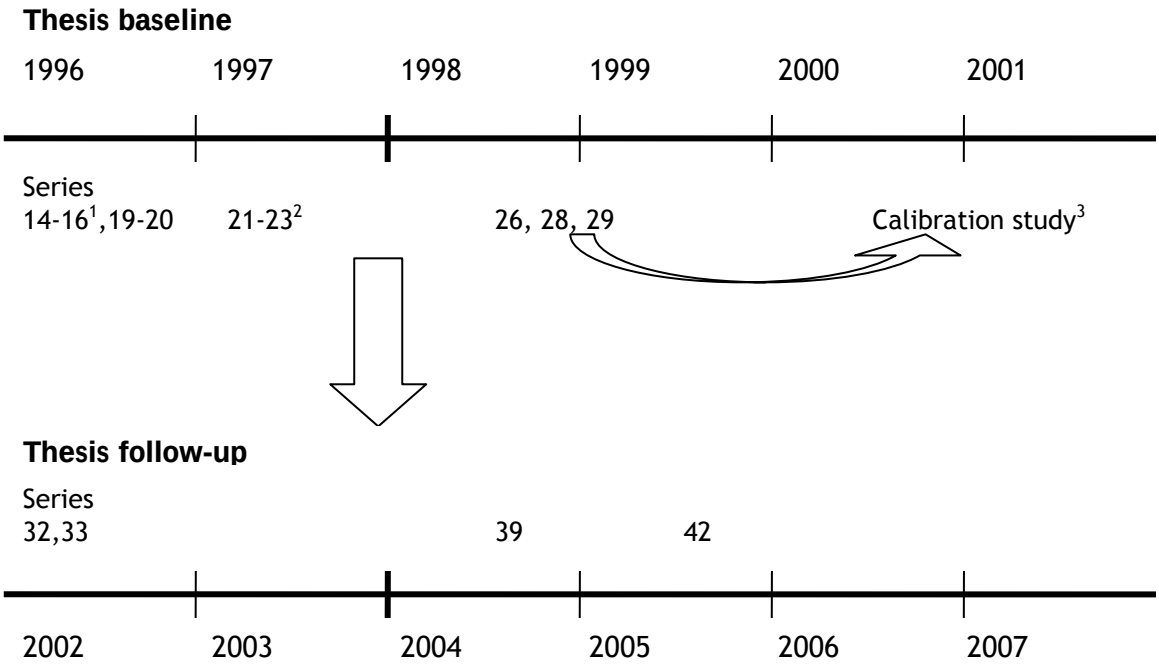


Figure 3.2: Enrolment in the NOWAC study. Adapted from Lund [97].

Figure 3.3 Timeline for included series and methodological studies



[1]Series 14 and 15 had 6 pages (all other questionnaires had 8 pages)

[2]Series 21 only included in paper 4

[3]Randomized selection from series 28 and 29, only included in paper 3

3.1.2 Dietary assessment and validation

Diet was assessed using a semi-quantitative food frequency questionnaire (FFQ). The dietary questionnaire was developed and validated against serum phospholipids by Hjartåker [101]. It was constructed to measure habitual diet the preceding year, with special focus on fish and marine products, but did not aim to capture the entire diet. The questionnaire is continuously being improved, and as new hypotheses have been developed, the food supply changed and need for clarifications have been seen, questions have been included, omitted or changed. To a large extent, this has been guided by various methodological studies. Table 3.1 shows the number of frequency questions in the different series.

A new validation, a comparison with repeated 24-hour recalls was performed in 2003 [99]. A test-retest study has also been performed [102] along with a study of how to handle missing values in dietary intake calculations [103].

Table 3.1 Number of frequency questions in the different series

Series	Number of frequency questions[1]
14, 15, 16	82
19, 20, 21	74
22, 23, 26	73
28, 29	85
32, 33	90
39, 42	113

[1]Frequencies of food, non-alcoholic and alcoholic drinks and dietary supplements

The results of these methodological studies were that the intake of marine products, particularly fatty fish and cod liver oil correlated well with the intake measured as content in phospholipids in serum [101]. The questionnaire's ability to rank participants was good for foods eaten frequently, and macronutrients expressed as percentage of energy intake [99]. For more infrequently eaten foods and some micronutrients weaker ranking abilities were seen. The reproducibility of the NOWAC FFQ is within the range reported for similar instruments, but may still attenuate estimates of disease risk [102]. As for missing values, a frequently encountered problem with FFQs, the methodological study in our material showed that null value imputation may lead to underestimation and misclassification of dietary intake, therefore testing of newer imputation methods was encouraged [103].

3.1.3 Dietary calculations

The dietary calculations were performed by a statistical program for SAS version 9.1 (SAS Institute Inc., Cary, NC, USA) developed at the Institute of Community Medicine, University of Tromsø for the NOWAC study [104]. The original program is constantly updated to reflect changes in the FFQ, changes in the food composition table and more effective programming. One notable difference is that the current version of the program uses edible portions directly instead of linking to the edible portions values in the food composition database for quantity calculations.

Through several steps the program transforms the frequency responses into frequencies per day, transforms portion responses into multiples of household measures or natural units when relevant, and takes seasonality into account. Some generic foods are split into more specific foods e.g. the question about apples/pears is split into 80% apples and 20% pears. The percentages are based on the 24-HDR data, sales data and common

sense. Then portion sizes and food composition database codes are assigned in order to link with the nutrient contents of the foods. Portion weights are largely adopted from a Norwegian table for household measures and weights for foods [105]. Some of the foods are summed up to get e.g. total amounts of fruits and vegetables consumed.

A dataset is created for quantities eaten (in grams per day), and finally the nutrient contents of all the foods are summed up and a dataset with nutrients intakes per day (in g, mg, µg, kJ or other, as appropriate) is constructed. Throughout the program several logical checks are applied to make sure that the calculations and linkages are correct. Some special programming is applied to certain foods, e.g. fat spread on bread where the participants can tick more than one type, and the quantity is a combined measure of how many slices of bread/crisp bread they eat and how thick a layer of fat they normally spread on.

For the thesis baseline calculations the 2001-version of the Norwegian Food Composition Database was used [106], while for the thesis follow-up calculations the 2006-version was used [107]. This was done in order to ensure that the most up-to-date values available were used, but simultaneously avoiding using new values on old food data, foods which composition might have changed. An example of a food which composition often changes is margarine; both the fat sources (mainly vegetable oils) and the processing methods (influencing e.g. content of trans-fatty acids) have changed over the last years. In general the values from the food composition database have been used unchanged in the thesis. However, the composition of cod liver oil has changed twice over the period these data were collected, so when cod liver oil has been included in the calculations, the food composition database has been updated locally to include values reflecting the composition at the time of data collection.

3.1.4 Non-dietary variables

The NOWAC-questionnaires contain questions on a wide range of non-dietary variables. For this thesis the following self-reported variables were used: physical activity (scale 1-10), weight, height, smoking (never, former, current), menopausal status (pre, post), number of persons in household, number of children, mother with breast cancer, use of postmenopausal hormone therapy (current, former, never), education (years), household income, region of residence, income, self-reported health and diet's importance for health. BMI was calculated as weight (in kilos) divided by the square of the height (in meters). In addition age at first birth and prevalence of certain diseases were tested as possible confounders. Prevalent diseases were also used as exclusion criteria (see 3.1.6).

3.1.5 Identification of cancer, vital status and emigration

The Central Person Registry keeps record of vital status and emigration [100]. At given intervals a request is sent to Statistics Norway for an update of the vital status of the participants, and to confirm that they are still residing in Norway. By using the national identity numbers, Statistics Norway also links with the Cancer Registry of Norway in order to obtain information about cancer diagnoses [4]. The information is returned to the NOWAC researchers using the serial number, not the national identity number.

3.1.6 Exclusion criteria

An overview of the exclusion criteria is given in figure 3.4. In papers 1 and 2 BMI was used as an adjustment variable, and participants with missing values on height or weight were excluded. In paper 1 physical activity was also an adjustment variable, and participants with missing values were excluded. Between the work on paper 1 and paper 2, a validation study of the physical activity scale against a combined heart-rate and accelerometer method was performed. Preliminary results suggested that the validity of the scale was relatively limited (unpublished data). In addition, the physical activity scale is one of the questions with the highest percentage of missing values in the questionnaire, and exclusions of those with missing values on physical activity would limit the sample size. We therefore decided not to use physical activity as an adjustment variable in the main analyses in paper 2, but rather performed a separate analysis with physical activity as an adjustment variable to check if it affected the estimates.

Also the exclusion criteria for implausible energy intakes differed between paper 1 and 2. In paper 1 the same criteria as was applied in the first food related papers from the cohort was chosen [104], while for paper 2 a more elaborate exclusion taking into account the relationship between energy intake and basal metabolic rate for the individual participant was chosen [108]. This criteria had been used in more recent NOWAC papers [109], and was also a response to a reviewer comment.

In paper 1 participants reporting high blood pressure, myocardial infarction, heart failure, stroke or diabetes were excluded. This was done because they were older and differed in energy intakes, physical activity and BMI compared to other participants. It was also assumed that these participants might have received individual dietary advice for their conditions, and it was interesting to investigate dietary choices after cancer diagnosis compared to dietary choices in the healthy population, which presumably has not received individual dietary advice. These exclusion criteria were not used for paper 2. High blood pressure, stroke and heart failure did not show good reproducibility when data from the

two questionnaires were compared (unpublished results). Also, age at diagnosis had a lot of missing, making it difficult to distinguish those who got these conditions before answering the thesis baseline questionnaire from those who got the conditions after answering the thesis baseline questionnaire. Therefore, it was decided to compare persons who got cancer with all cancer-free persons, including those who suffered from various other conditions.

Prevalent cancer cases were included in paper 1 and excluded from paper 2 and 4. Paper 4 concerns cancer patients, and all participants who were free from solid tumours until 01.01.07 were excluded. Participants with missing information on cancer stage, smoking, cod liver oil or other dietary supplements were also excluded. Finally, those who were diagnosed upon death did not contribute person-time to the analyses and were excluded. Exclusion criteria for paper 3 are explained in paragraph 3.2.3.

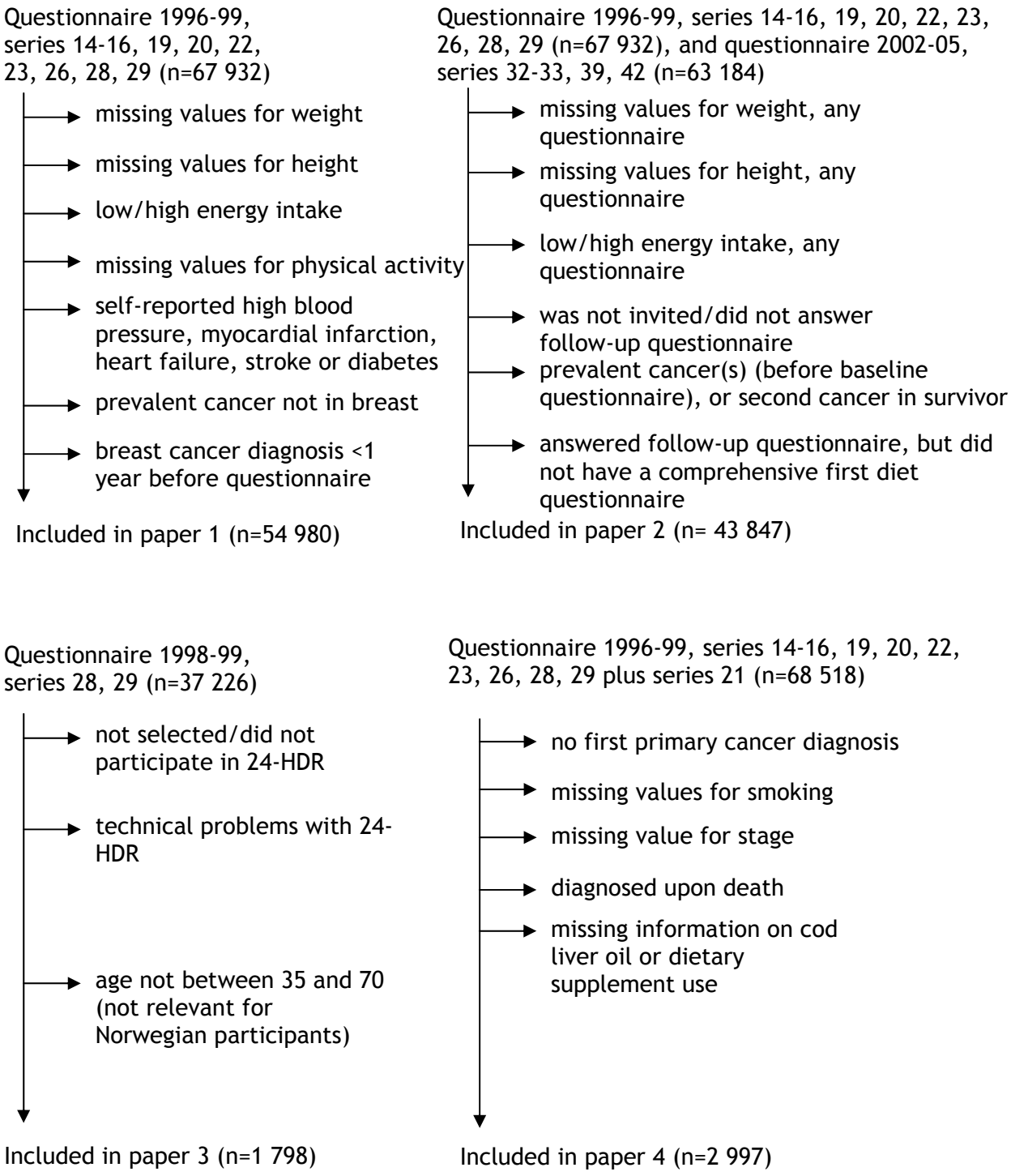


Figure 3.4 Comparison of inclusions and exclusions in the papers. Arrows pointing to the right signify exclusions

3.2 The European Prospective Investigation into Cancer and Nutrition

The European Prospective Investigation into Cancer and Nutrition (EPIC) started in 1992 and is a prospective multi-centre cohort study with 23 centres in 10 countries; Norway, Sweden, Denmark, The Netherlands, the United Kingdom, Germany, France, Spain, Italy and Greece [110]. The overall aim of the study is to investigate the relationship between diet and cancer. The large variation in cancer rates and dietary habits in the countries included in the study together with its large size help overcome many methodological problems with earlier studies. The EPIC study has evolved to study other diseases as well, and the size now allows for analyses of interactions between nutritional, genetic, hormonal and lifestyle factors.

More than half a million participants are included in the cohort (366 521 women and 153 457 men), most of them aged 35-70 years at recruitment [111]. The majority of the sub-cohorts were recruited from the general population residing in a given geographic area, with some exceptions. The French cohort consists of members of a health insurance program for school workers, half of the Oxford cohort in UK consists of vegans, vegetarians and other "health-conscious" persons, some of the Spanish and Italian cohorts consist of blood donors and their spouses, and the Utrecht (the Netherlands) and Florence (Italy) cohorts consist of women participating in mammography screening programs [110]. The French, Norwegian, Utrecht and Florence cohorts only recruited women.

3.2.1 Ethical issues

All participants consented to be included in the study, and the studies were approved by the ethical committees at the participating institutions and at the International Agency for Research on Cancer which coordinated the study [110].

3.2.2 Dietary assessment

The baseline dietary assessment was performed with country-specific dietary assessment methods [112-115]. In most countries self-administered food frequency questionnaires of varying length were used, but some combined two methods [110]. In UK a semi-quantitative FFQ and a 7-day record was used, and in Malmø a short non-quantitative FFQ with a 14-day record of hot meals was developed. In some of the Southern European centres the questionnaires were administered by interviewers. Data from the baseline dietary assessment have not been used in this thesis, and will not be discussed further.

Since the dietary assessment methods differed between countries, a second, common dietary assessment was carried out in a sub-sample of the cohort in order to adjust for differences due to assessment methods rather than real intake [113]. The calibration sub-cohort consisted of between 5 to 12% of the population in each national cohort, except in UK where a sample size of 1 117 (≈1.5%) was chosen to provide population-level calibration. The second dietary assessment method was single 24-HDR, and a computerized 24-HDR software, EPIC-Soft, was developed to standardize dietary intake reporting across study sites, and to increase the likelihood that the measurement errors would be of a similar magnitude and nature in all study centres [116,117]. The EPIC-Soft program had country-specific food lists and portion sizes, but information was collected in the same structured manner. A picture book(let) was used to aid in food quantification. Interviews were performed face-to-face at the study centres, except in Norway where telephone-interviews were used [98]. A comparison showed that telephone vs. face-to-face interview design did not influence recalled diet [98]. Food intakes from the 24-HDR have been reported elsewhere [118].

At the end of the interview a question about dietary supplements was asked: *"Did you take any vitamins…?"* The question was rather open, and only specified vitamins, but the country-specific supplement lists specified products beyond vitamins such as garlic and fish oil. A question about the physical state of each supplement was asked (e.g. liquid, tablet or injection), and the intake was quantified. The set of questions was repeated until all supplements taken were documented, and there was no upper limit on the number of supplements one participant could report, and products not included in the pre-specified lists could be added.

3.2.3 Non-dietary variables, exclusions and participation rates

Information about age, whether the participant followed a special diet, and whether the recalled day was a special day with regard to diet was collected during the 24-HDR, and was complete for all participants. Self-reported health was taken from the baseline assessment. As it was not among the core questions, it was not available from all centres. Prevalent cancer status was taken from the last cancer up-date before the 24-HDR. Some countries had prevalent cancer as an exclusion criterion, and prevalent cancer cases from these countries were therefore not included in the analysis on cancer status and supplement use. Information about cancer is obtained in different way in different sub-cohorts, most use cancer registries, some use a combination of methods including health insurance records, cancer and pathology registries and active follow-up of participants or next-of-kin [110].

Approximately 1% of the interviews performed were excluded, mainly due to technical problems locally, although some interviews were also excluded e.g. because the participants' baseline data were incomplete [113]. The age ranges of the participants in the EPIC baseline study differed between sub-cohorts. Consequently, the age ranges in the calibration study also differed between sub-cohorts, but most participants were between 35 and 74 years old, and those outside this age range were excluded from the analyses in paper 3. In addition, some participants (<1% of the final sample) were added to the calibration study, these were involved in other EPIC cross-sectional or validation studies and most of them were sampled from the calibration sub-populations [113]. The participation rates in the local centres varied from 46.5% to 92.5%, but except in Greece and the UK the all countries had participation rates above 60%. In Norway 61% of the approached women participated [113].

3.3 Dietary supplements

There is no commonly agreed definition of dietary supplements [53,119]. The meaning of the word may differ both between countries, within countries and over time. In paper 3 it was decided to use the EU regulatory definition as guiding definition, despite that this definition was adopted long after the data collection [120]. The question asked to the participants in the EPIC calibration study only specified vitamins, but the pre-specified supplement lists show that there must have been a broader, but maybe not very clear, definition as basis for the assessment. Papers from the baseline studies in several of the EPIC centres showed that supplement use was more than just vitamins e.g. [56,71,72,121]. This prior knowledge also helped deciding on a supplement classification [122], which mainly took the main ingredient(s) into account. For EPIC, it was not considered feasible to construct a dietary supplements database long after the actual consumption had taken place, and consequently no attempt to quantify the nutrient intakes from the supplements were made.

The questions on dietary supplements asked in the NOWAC study has changed over time. In general, separate questions have been asked about cod liver oil, other fish oils and other dietary supplements (see annex II for examples of all the supplement questions). In some series cod liver oil and fish oil could be reported by a closed list of brand names (plus an option for "other"). In other series no brand name information was asked, only frequencies and in yet other series an open question was asked.

For other supplements only a frequency question and a question on brand name(s) were asked in some series (14-16, 19-21, 32-33), whereas in other series (22, 23, 26, 28,

29, 39 and 42) there was a conditional yes/no question before the frequency question. In some series (22, 23, 26, 28, 29) an example (vitamins, minerals) was used, in most series not.

3.4 Cancer survivors

Research on diet and cancer survivors is a relatively new discipline [3,10], and not much has been done in Norway [123]. The NOWAC study was not originally set up to study cancer survivors, so some methodological challenges arise. Ideally all survivors should have been sampled at a given, restricted time since diagnosis, preferably at diagnosis or e.g. after completed treatment [21]. This could have been done in a nested case-control study. Such a study is actually going on in the cohort; breast biopsies and supplementary blood samples are collected at cancer diagnosis, and age-matched cancer-free controls from the cohort are asked to donate blood [97]. However, in order not to burden the participants they are not asked to fill in the NOWAC questionnaire, just a short questionnaire on factors that might affect blood levels.

Variables related to treatment would also have been relevant to include in the analyses for paper 1, 2 and 4. Information on whether the cancer survivors were in active treatment or not when completing the questionnaire, and which type(s) of treatment they have been given could have informed the analyses. Some of the colorectal cancer survivors in paper 2 have probably had surgical treatment where parts of the gut have been removed, and this could affect their diet and nutrient absorption [124]. A national clinical registry for colorectal cancer has only recently been established [5], and does not cover the majority of our cases [5].

3.5 Statistical analyses

All analyses were performed using SAS release 9.1 (SAS Institute Inc., Cary, NC, USA).

In papers 1 and 2 analyses of variance (ANOVA) were used to describe difference between breast cancer survivors and healthy women. This was done with the general linear models procedure in SAS. Multiple adjusted analyses were performed; hence type III least square mean estimates (mutually adjusted) were used. Post-hoc Bonferroni tests were used to determine which of the groups differed when significant differences were found in the anova analyses. Pairwise comparisons and stratified analyses were performed in order to further describe the differences and similarities in diet and lifestyle. Due to the large number of analyses the level of significance was set to $p< 0.01$.

Paper 3 will appear in a supplement issue on nutrient intakes in the EPIC calibration study, and a guideline for some common statistical analyses for all papers in that issue has been developed [125]. This guided the analyses, but some adaptations were made. Dietary supplement use was uncommon in some countries, and in order to increase the precision in the estimates it was decided to present data on gender and country level, not centre level as recommended in the guidelines. Adjusted mean percentages and standard errors at the country level were calculated using generalised linear models. The models were weighted for sampling differences in seasons and weekdays *vs.* long weekend at the centre level. The overall estimates were adjusted for age as a continuous variable, while the age-specific estimates were stratified by 10-year age classes. Since there were few users and/or participants in some strata (particularly for men), the age-adjusted overall estimates were outside the range of the age-stratified estimates in some of the countries. This was because of the low precision in some of the estimates, and not because of real statistical differences. Analyses including only supplement users were based on crude data, as weighting among users would have removed the effect of seasonal and weekday variation in supplement use. Overall gender differences were tested in anova analyses, and age differences by centre and gender were tested in a regression model with age in 10-year age groups as the predictor variable. Stratified analyses were performed for diet and health-related variables. P-values less than 0.05 were considered significant.

In paper 4 the Cox proportional hazards model was used to calculate hazard ratios for mortality with corresponding 95% confidence intervals. Assumptions for the Cox proportional hazards model were tested and met. Time since diagnosis was used as the primary time-variable. Kaplan-Meier plots were constructed to describe the survival function. Survival differences between groups were assessed for statistical significance by the log-rank test. Differences between categories of cod liver oil and other supplement use were tested in analyses of covariance and Cochran-Mantel-Haenszel's test adjusted for age at diagnosis. The level of significance was set to $p< 0.05$. The associations between cancer survival and cod liver oil and other dietary supplements use respectively were first examined in age-adjusted analyses. A set of potential confounders were tested individually in a model with age and supplement use, and whenever a significant change in risk by supplement use was observed, the variable was included in the multivariate models. If the estimate for supplement use in the multivariate adjusted model changed 5% or more when a confounder was included, it was kept in the model. Interaction between smoking and dietary supplement use was tested by including an interaction term in the models for total cancer.

4 Results – summary of papers

Paper 1

Diet among breast cancer survivors and healthy women. The Norwegian Women and Cancer Study

The paper describes diet and lifestyle of breast cancer survivors and healthy women in a cross-sectional subset of the NOWAC study, and explores differences by time since diagnosis, by comparing short-term (five years or less) and long-term (more than five years) survivors.

Among women aged 41-70 years who answered a questionnaire with dietary information in 1996-99, the Cancer Registry of Norway identified 314 short-term survivors with 1-5 years since diagnosis and 352 long-term survivors with more than 5 years since diagnosis. These women were compared with 54314 women free of cancer, diabetes, myocardial infarction, stroke, high blood pressure and heart failure.

Overall there were few differences in the diet of the three groups. Short-term survivors ate more fruits (217 vs. 181 g) and vegetables (143 vs. 124 g) than healthy women ($p<0.001$), and consumed more of nutrients associated with this food group (fibre, mono- and disaccharides, folate, vitamin C and potassium). The percentage of dietary supplement users was higher (72% vs. 61%, $p=0.003$) and the level of physical activity was lower among short-term survivors than among healthy women (5.2 vs. 5.5, $p=0.01$). The long-term survivors did not differ from any of the other groups. In conclusion: Diet and lifestyle was generally similar between breast cancer survivors and healthy women, especially more than five years after diagnosis.

Paper 2

Dietary change among breast and colorectal cancer survivors, and cancer-free women in the Norwegian Women and Cancer cohort study

The objective of this study was to investigate diet before and after diagnosis of breast and colorectal cancer compared with diet in cancer-free women in the NOWAC study.

The paper reports dietary changes from a data collection in 1996-99 to another in 2002-05. 43847 cancer-free women aged 41-70 years answered the baseline questionnaire and follow-up questionnaire on diet and lifestyle. Of these, 130 women developed colorectal cancer and 563 breast cancer between questionnaires. Dietary change in the

three groups was compared, and for breast cancer a comparison was made according to stage and time since diagnosis.

Breast cancer survivors increased fruit and vegetable consumption with 81 g compared to 42 g in colorectal cancer survivors and 50 g in cancer-free women. Milk consumption was stable in colorectal cancer survivors, and decreased in cancer-free women. Significantly more cancer survivors quit smoking. There were no differences in change of alcohol consumption or BMI between the groups. In breast cancer survivors, most changes occurred more than 2.4 years after diagnosis, and stage II survivors made larger changes than stage I survivors.

In conclusion: cancer survivors seemed to follow general dietary and lifestyle trends, and did not modify well-established cancer risk factors as alcohol and high body mass more than cancer-free women did.

Paper 3

Use of dietary supplements in the European Prospective Investigation into Cancer and Nutrition calibration study

The aim of this study was to describe the use of dietary supplements in subsamples of participants from the 10 countries in the European Prospective Investigation into Cancer and Nutrition.

Specific questions on dietary supplement use were asked as part of single 24-HDRs performed on 36 034 men and women aged 35-74 years from 1995 to 2000.

Between countries the mean percentage of dietary supplement use varied almost 10-fold among women and even more among men. There was a clear north-south gradient in use, with higher consumption in the northern countries. The lowest crude mean percentage of use was found in Greece (2.0% among men, 6.7% among women), and the highest in Denmark (51.0% among men, 65.8% among women). Use was higher in women than in men. In Norway 61% of the participants reported dietary supplement use. Vitamins, minerals or combinations of them were the predominant types of supplements reported, but there were striking differences between countries. Dietary supplement use seemed to be more common in persons with prevalent cancer than in cancer-free persons, but samples were small.

This study indicates that there are wide variations in supplement use in Europe, which may affect individual and population nutrient intakes. The results underline the need to monitor consumption of dietary supplements in Europe, as well as to evaluate the risks and benefits.

Paper 4

Cod liver oil, other dietary supplements and survival among cancer patients with solid tumours

Survival of cancer patients with solid tumours in the NOWAC study was explored in relation to supplement use before diagnosis. We performed Cox proportional hazards analyses, adjusting for age at diagnosis, smoking and stage.

Cod liver oil was the most frequently used dietary supplement, followed by multivitamins and –minerals. Before diagnosis, 46.4% of the patients were cod liver oil users, and 57.1% used other dietary supplements. Whole year daily use of cod-liver oil was associated with lower risk of death in patients with solid tumours (RR 0.77, 95% CI 0.61-0.97) and in lung cancer patients (RR 0.56, 95% CI 0.34-0.92). Also daily and occasional use of other dietary supplements decreased the risk of death among lung cancer patients (RR 0.70, 95% CI 0.49-0.99 and 0.55, 95% CI 0.31-0.97).

More research is needed in order to clarify the association; meanwhile adjustment for dietary supplement use should be performed in survival analyses of lung cancer patients.

5 Discussion

Issues related to study design and validity will be discussed before the results.

5.1 Study designs

Different study designs might help illustrate a scientific issue in different ways. This section discusses and compares the study designs used in this thesis and highlights some of their strengths and limitations. Some alternative approaches are also discussed.

5.1.1 Cross-sectional versus prospective studies

In paper 1 a cross-sectional design was used, while in paper 2 a prospective study design was used. Cross-sectional studies provide information on exposure (prevalent cancer) and outcome (diet) without information on the temporal relationship between them, since all information is collected at one point of time. Therefore, cross-sectional studies cannot inform us about causal relationships, but can suggest presence or absence of associations between exposure and outcome [126]. Paper 1 indicated that there were differences in the diet of breast cancer survivors and cancer-free women, and that it was relevant to pursue the analyses in a more elaborate design. In the prospective design the time-effect relationship is established, as the exposure (incident cancer) is measured before the outcome (change in diet from pre- to post-diagnosis) [127]. However, chance, confounding and bias might still distort the associations.

One of the aims of this thesis was to describe dietary change in cancer survivors compared to cancer-free women. For this the prospective design is superior, however, most studies to date have used a cross-sectional or retrospective design [39].

5.1.2 Transformed cohort studies versus dedicated survivor cohorts

Doing survivor research in a traditional cohort, a transformed cohort design, has some limitations. One alternative to studying cancer survivors in a cohort designed for other purposes would be a cohort of survivors only, a dedicated survivor cohort. This design has some possible benefits [21]. First, all participants could be enrolled at a uniform time (period) since diagnosis. Second, baseline diet is measured after diagnosis, and third, follow-up could be done at specific intervals after diagnosis, not at given calendar times. This means that presumed critical periods can be more uniformly studied, but it requires rapid case ascertainment in order to enrol potential participants soon after diagnosis [21].

Updates via cancer registries typically take months or years, and may therefore not be rapid enough.

Many of the above mentioned benefits can be compensated for within a transformed cohort. Regular repeated measurements can limit time between diagnosis and enrolment, and can also help cover critical periods [21]. Actually, since update of cancer status takes time, unless one is in a clinical setting, a transformed cohort study might include survivors sooner after diagnosis than a dedicated survivor cohort. In paper 2 we took advantage of the repeated measurements in the cohort. Mean time since diagnosis was 2.4 years for breast cancer survivors. In Norway cancer incidence and survival is released annually from the Cancer Registry, with a lag of approximately 13-25 months between diagnosis and publication of numbers. Consequently, enrolment at a uniform time close to date of diagnosis would have been impossible unless special arrangements had been made with local hospitals. For breast cancer this might not be that critical, but for cancers with low survival rates, such as lung cancer, the lag between diagnosis and enrolment introduces substantial survival bias (see 5.2.1). Anyhow, for such cancers, the effect of post-diagnosis diet or changes in diet might be less important than the pre-diagnosis diet. If post-diagnosis diet is of more concern, one can study prevalent cancer cases in the cohort, unless they were excluded from the study. In NOWAC, prevalent cancer is not an exclusion criterion, and paper 1 is an example of this kind of analysis. However, such an approach will most likely suffer from survival bias.

Transformed cohorts are only an option for frequent cancers. For rarer cancers transformed case-control studies is a possibility. When converting case-control studies into survivors studies many of the same challenges as with transformed cohort studies exists, and rapid case ascertainment and periodic follow-up might help overcome some of them [21].

Newly established survivor intervention studies have not always taken advantage of the possible design benefits mentioned above: The WHEL study enrolled women up to 4 years after diagnosis [46], while the WINS study restricted enrolment to those 1 year or less after diagnosis [45]. In survivor cohorts enrolment have taken place e.g. within 2 months [128], at 6 months [21], 4-12 months [129], approximately 9-15 months [21], 10-11 months [40], and on average 2 years [24] after diagnosis. Follow-up is scheduled at uniform calendar times [21,24,129] or at given periods since diagnosis [21,40,128]. Most of these studies have chosen to include only early-stage survivors. As a result of these choices, many of the survivor studies are not more standardized than studies done within a traditional cohort design.

Dedicated survivor studies might be superior for some aspects of prognosis research, but it might not be the case for all aspects of cancer survivorship research. Many early studies of cancer survivors suggested that the practice of healthy lifestyle behaviours was higher in cancer survivors than in the general population, but these studies often lacked a comparison group from the general population [14]. When such comparative studies have been done, the differences between survivors and the general population has generally not been very large [22,25,27]. Paper 1 and 2 add to this picture.

Since many of the cancer survivor studies have been cross-sectional, we cannot rule out that the survivors have made changes from unhealthier pre-diagnosis habits. It has been speculated that lifestyle changes could have been of a more temporary character, or that the results from previous studies might not generalize to all survivors [14]. Therefore, studies with population controls also have their place in the cancer survivorship field, and repeated measurements are helpful in elucidating the process of change, and potential relapse to old, pre-diagnosis habits. Traditional cohort studies might also provide information about the change process quicker, by taking advantage of the different length of period between diagnosis and follow-up questionnaires. This has been done both in paper 1 and 2, where dietary change in breast cancer survivors was evaluated according to time since diagnosis.

Survivor cohorts will often have better data on medical and treatment issues, and have the possibility to use more targeted questions relating to the cancer experience. If they are conducted at major cancer centres, rather than by mail or telephone, they may not be representative of minorities, poor, rural and other hard-to-reach populations, particularly in countries where free health-care is not available for all [40]. Most survivorship studies concentrate on one single cancer site, usually the most frequent ones, making comparison between different cancers difficult [40]. Possibly the ideal design for studies of frequent cancers would be a nested case-control study in the cohort, with access to medical records for tumour and treatment specific information, extra questionnaires to the survivors related to their disease, but also with questionnaire(s) to cancer-free controls in order to keep the comparison with the general population.

5.1.3 24-hour dietary recalls

In the EPIC calibration study, dietary supplement use status was assigned based on the reported use on one single day. For data on the individual level, this is a highly unsatisfying study design. For individual data on nutrients the number of days needed per person for 95% of observed values to lie within 80% of the true mean varies enormously from nutrient to nutrient, e.g. from 4 days for total fat (energy-adjusted) to 106 days for vitamin A

(energy-adjusted) [130]. However, the aim of the present study was not to give individual estimates, but to provide comparable country-specific estimates. Given the many problems with dietary supplement definitions, reference periods, duration and content (cfr. 3.3 and 5.2.2.3) it is considered that a single 24-HDR is a sufficient design for reaching the aim of the study, and superior to using EPIC baseline data, mainly collected from various FFQs. Since the results were weighted for season and weekday vs. weekend interviews, potential differences in patterns of use between countries should not confound the results.

If information on the individual level is sought, more than one recall should be collected per participant. An American study found that in comparison with a brief questionnaire, three recalls could accurately and reproducibly capture data on supplement use for frequently consumed products, but might perform less well for products used less often or more intermittently [131].

5.2. Validity

A study is considered to be valid if the findings can be taken as being a reasonable representation of the true situation [127]. Three factors generally compromise the validity of study findings; selection bias, information bias and incorrect use of statistical methods including failure to take confounding factors into account [132]. The term internal validity refers to the ability to draw conclusions regarding the study population [132]. External validity refers to the potential to draw conclusions also for other populations [132]. A debate about validity of dietary assessment methods in general, and FFQs in particular has been going on for years (e.g. [133,134]). The discussion of the validity of the NOWAC FFQ will concentrate on this specific FFQ, and not the method in general.

5.2.1 Selection bias

Selection bias occurs when there is a systematic difference between the characteristics of the individuals selected for the study and the characteristics of those who were not [126]. The methodological studies done in NOWAC have shown that women not born in the Nordic countries had lower response rates, women living in Northern Norway had higher response rates, and that the response rate dropped with increasing age [96]. Linkages to the Norwegian fertility registry and the registry of education showed that the participants were younger, fewer were nulliparous or uniparous, but the proportion of women with three or more children were approximately the same as in the source population. Responders had a slightly higher age at first birth, and a higher percentage had more than 12 years education compared with the source population.

No difference was found in the distribution of self-reported parity, ever use of oral contraceptives and years of education in non-responders (who participated in a non-respondent study) and responders from the same series [96]. Reasons for non-participation were e.g. worries about confidentiality, lack of time or interest, and simply forgetting about it. Data from the Cancer Registry of Norway showed that cumulated incidence rates in the NOWAC study and in all Norwegian women of the same age were almost identical both for all cancer sites combined as well as for breast cancer [96]. Therefore, although only 57% of the invited women responded to the NOWAC baseline questionnaire and the participants were somewhat younger and better educated, the conclusion was that no major selection bias that would invalidate the calculation of population attributable risk was found [96].

The participation rate corrected for death and emigration at the first NOWAC follow-up questionnaire was 81%. Since there may be selection bias from baseline to follow-up, participants responding to the NOWAC follow-up questionnaire were compared with all women responding to the NOWAC baseline questionnaire regarding the information given at enrolment. Almost no differences were found in the comparison, but those who completed the follow-up questionnaire were slightly younger (46.4 vs. 45.9 years) and slightly better educated (11.8 vs. 12.0 years) [97]. This suggests that combining data from the NOWAC baseline questionnaire and the first NOWAC follow-up questionnaire to form the thesis baseline did not lead to selection bias.

Even though selection bias does not appear to be a problem in general, there might be selection bias among the cancer survivors. This bias could go both ways, cancer survivors could be ill/under treatment, and less able or interested in participating in anything reminding them of the disease. Or, cancer survivors could be more motivated to participate in a cancer study than cancer free-women. Corrected for death and emigration, participant rates in series 28 were 82.1% among cancer-free participants originally enrolled in series 1-5, and 82.6% among those who developed cancer. For thesis baseline compared to thesis follow-up the total participation rate was 76.4%, among cancer survivors it was 74.2%. There is therefore no reason to believe that there is more selection bias among cancer survivors than among other participants. It has been demonstrated that the response rate was higher when the study was called “Women and cancer” than “Oral contraceptives and cancer” or “Women, lifestyle and health” [135]. One selection bias is obviously present in our study, namely the survival bias. Both in papers 1 and 2 (and 3) the survivors included are healthier than the total sample of survivors, since survivors who died before receiving the questionnaire were not eligible. As

survival rates are lower for colorectal cancer than for breast cancer, this might have affected the survivor groups in paper 2 differently.

For the EPIC baseline study, selection bias is not possible to assess correctly. Although most of the sub-cohorts were representative for persons residing in specific area, this was not the case for all of them [110]. Some sub-cohorts sampled people engaging in health related practices e.g. mammography program participants, blood donors or so-called "health conscious" people. It is likely that these participants are more health conscious than the average, and that there is a so called healthy volunteer bias in the cohort [132]. Some of the sub-cohorts could not enumerate the invited population, and had no possibility for calculating response rates and difficulties making comparisons with the source population [110]. At the country level between 54.2% and 91.6% of the subjects selected for 24-HDR, actually participated. A slight tendency of underrepresentation of current and former smokers, and persons with low education compared to in the baseline sample was seen, so selection bias cannot be ruled out, but it was concluded that the calibration sample is fairly representative of the baseline cohort [113].

5.2.2 Information bias

Information bias arises when the study subjects consciously or unconsciously give incorrect information, or the wrong information is recorded by study personnel or instruments [132]. The food information might be biased, as the accuracy of filling in questionnaires varies. Recall bias occurs when reporting differs according to disease status. In paper 1, it is possible that the breast cancer survivors reported their diet more accurately than the healthy women. Similarly, at follow-up in paper 2 the survivors might have filled in the questionnaire more accurately than the cancer-free women, but at baseline no difference in accuracy of reporting is expected in a cohort study. In dichotomous variables, misclassification will lead to attenuation of risk, and give estimates closer to zero, but in non-dichotomous variables such as most food data, the effect of the measurement errors is more unpredictable, though if measurement error is non-differential, the result is usually attenuation of risk estimates [132].

5.2.2.1 Cancer and vital status

In 2007 a special issue on data quality in the Cancer Registry of Norway was published [4]. The percentage of cases verified based on death certificate only was low, about 0.9% overall. The proportion of cases registered with primary site unknown has been stable over the period 1971-2005, around 3% of the cases [4]. Only 13% of the lung cancer cases, 9% of the colon cancer cases and 0.5% of the breast cancer cases were diagnosed with unknown

stage. The estimated overall completeness for the period 2001-05 was 99.7% [4]. The case registration is considered to be highly valid, which means that exposure assessment in paper 1 and 2 (prevalent and incident cancer) is valid.

Death notification is mandatory and reports are sent at least quarterly to the Central Person Registry. The registry is virtually complete, and the vital status is assumed to be highly valid [100]. Therefore, outcome (vital status) in paper 4 is highly valid.

5.2.2.2 Diet and dietary change

The validity of the NOWAC FFQ has been studied both in relation to a biomarker [101] and an independent dietary assessment method, 24-hour dietary recalls [99]. Reproducibility over a three month-period has also been studied [102]. These studies showed that the validity and reproducibility of the NOWAC FFQ is within the same range as in similar studies. The 24-HDR validation study also evaluated FFQ data from 1998 with 24-HDR data from 2002-2003, and found largely the same results as for the FFQ data collected in 2003 [99]. The questionnaire has good ranking abilities, especially for foods eaten frequently and for macronutrients. However, as with all dietary assessment methods, there are measurement errors, and caution must be taken in interpreting the results.

The 24-HDR validation study showed that the validity of estimates of milk and milk products, coffee and alcoholic beverages is good, even though the latter two were underestimated in the FFQ [99]. For fruits and vegetables the validity was fair, both food groups were overestimated in the FFQ compared to the 24-HDR. Misclassification into extreme quintiles occurred only in 2 and 1% of the occasions. The effect on the results in this thesis is probably that the absolute values of the change in fruits and vegetables is overestimated, while for milk and milk products it is fairly correct, and for coffee and alcoholic beverages it is underestimated. The relative change (e.g. change as a percent of baseline intake) should not be much affected.

The three-month reproducibility study showed good results for the above mentioned food groups (e.g. Spearman correlations coefficients above 0.7). Still, in a simple analysis of the association between alcohol intake and the risk of hypertension the risk estimates were attenuated compared to the estimates calculated from the calibrated alcohol value [102]. The situation in paper 2 is much more complex; there are both adjustment variables with measurement error (e.g. BMI and baseline diet) and exposure variables without measurement error (cancer diagnosis, age and type of questionnaire), and measurement error in the outcome variables (dietary change). Therefore, it is not straightforward to predict how calibration would have affected the results in this paper [136].

The reason for sending out repeated questionnaires to participants is to update exposure information (e.g. dietary intake). One seeks to find out if the participants continued, discontinued or modified their lifestyle practices. A certain degree of stability is expected, and a follow-up study can also be seen as a long-term reproducibility study. The observed change is a combination of measurement errors and actual change. Long-term reproducibility studies with FFQs (e.g. five years) have found correlation coefficients ranging from 0.41-0.77 in foods [137] and 0.42-0.90 in nutrients [138]. These studies concluded that there was good agreement between the measurements.

A Japanese study with a 33 item FFQ found lower correlations and concluded that there were considerable changes in food intake over five years [139]. In addition to the food questions on follow-up, there was a question on subjective change for each food (no change, increased or decreased consumption). Subjective difference and longitudinal difference calculated from the change scores of the frequencies were poorly related, the direction of the change was inconsistent for more than half of the items. This shows that subjective change information might be incorrect, and repeated measurements probably give more precise information.

Given the changes made to the NOWAC questionnaire, both within the thesis baseline, within the thesis follow-up and between thesis baseline and follow-up, long-term absolute reproducibility for some foods and many nutrients would most likely be rather low. For nutrients and food groups it is still possible that the ranking of participants would be satisfactory. The aim of the thesis was not to study the general trends in dietary intake in Norway, but to compare changes in dietary intakes in cancer survivors and cancer free-women. Therefore, unless there is an interaction between cancer status and type of questionnaire, the differences in change should not be affected by the changes in the questionnaires. However, such an interaction might actually exist, since there is an interaction between age and cancer, and mean age among participants from series 14-23 was higher than among participants from series 26-29. Since age and type of questionnaire was adjusted for in the analyses both in paper 1 and 2, we assume that the effect on the results was minimal.

5.2.2.3 Dietary supplements

The dietary supplements questions in the NOWAC study have been changed several times, partly to increase the validity, e.g. remove obsolete brand name options for cod liver oil and other fish oils capsules, and to give more room for brand names for other dietary supplements. Lay-out changes have improved readability, which should decrease missing values, and in some series a conditional yes/no question on use has been used so that non-

users could skip irrelevant questions. Two conclusions can be drawn from the cod liver oil questions: first, the supplement market is very dynamic, and brand name information is quickly getting obsolete. Second, many participants have problems distinguishing between cod liver oil and other fish oils. With open questions both for cod liver oil and fish oil, there was a considerable element of misreporting, e.g. cod liver oil was reported as fish oil and vice versa (unpublished results from an independent series where brand names were coded).

Both the format and the wording of the questions on other dietary supplements have also changed. As can be seen from table 5.1, this affected the prevalence of use.

The changes made, both the inconsistent use of conditional questions, and the omission of examples of dietary supplements, probably harmed validity, as seen by the falling number of users between 1998/99 and 2004/05 (table 5.1). Given that the sales more than doubled in the period [55], change calculations would most probably not have been valid, and dietary supplements were therefore not included in paper 2. Even though there were some differences in the supplement questions at baseline, there is no reason to believe that this should affect the cases and cancer-free women differently, but it adds to the imprecision in the estimate of users. Participants with missing answers on all questions were classified as non-users. Those who reported name, or answered yes to the conditional question, but no frequency, were assigned missing values. Therefore the estimate of users is a conservative one, and most likely underestimated. The prevalence at thesis follow-up indicates that the underestimation is larger in series without conditional questions.

A problem when comparing dietary supplement use between studies is how frequency and duration of use has been recorded [53]. In the EPIC calibration study dietary supplement user status was determined based on one single day. Even if this does not reflect habitual use, group level estimates are assumed to be valid. No information was collected on duration or frequency of use. In the NOWAC study the participants are asked to think about the last year when they fill in the questionnaire, but no specific questions on duration are asked [56]. The EPIC baseline cohort queried supplement use in different reference periods in different countries, e.g. least four weeks during the past year [72,75], at least three times a week [76], and at least once during the seven days recorded [140]. Consequently, even though the EPIC baseline information reflected use over a longer period than the 24-HDR, a comparison of dietary supplement use at baseline would have been difficult, not only due to different definitions, but also due to the different reference periods for supplement use.

Table 5.1: Prevalence of use of dietary supplements other than fish oils according to different types of questions

Series at thesis baseline	Timing of thesis baseline	Age at thesis baseline	Questions at thesis baseline, example[1]	Prevalence at thesis baseline (%)[2]	Series at thesis follow-up (timing)	Questions at thesis follow-up example (y/n)[1]	Prevalence at thesis follow-up (%)[2]
14-16, 19-20	1996	45-69	Frequency, brand name	37.3	32-33 (2002)	Frequency, brand names	41.5
22,23	1997	45-69	Conditional, frequency, brand name	52.5	32-33 (2002)	Frequency, brand names	41.9
26,28,29	1998-99	41-55	Conditional, frequency, brand name, example	52.5	39,42 (2004-05)	Conditional, frequency, brand names	35.6

[1]Brand names were coded as 1 if reported, else missing in thesis baseline. Thesis follow-up was optically read, and open ended variables on brand-names were not coded.

[2]Prevalence among all participants with valid answers. Users were defined as those reporting a frequency higher than once a month. If all questions on supplements were left open, or the answer to the conditional question was no, the participant was considered a non-user. If no frequency was given, but some other information suggesting use, the participant was considered as having missing data, and not included in the prevalence estimates.

No validation has been done on the EPIC dietary supplements data, but a crude comparison with published results from the local study centres showed prevalences in the same range as the calibration study [56,76,140-142], except in Spain [143] where use tended to be lower, and Germany where use tended to be higher in the local studies [72,75].

5.2.3 Statistical validity including confounding factors

Diet and several lifestyle factors are related [104], therefore adjustment for possible confounding effects are important in diet-cancer analyses. In order to include a large number of adjustment factors in the analyses, particularly categorical factors, a large sample size is needed, and all groups compared must be quite large, as the entire distribution of all adjustment factors should be represented for all subgroups. If some of the subgroups are too small, or if a value on one of the adjustment factors is not represented in one of the groups, the analyses break down. For this reason, it was a priori decided to limit the number of adjustment factors in papers 1 and 2, and not to check for interactions, as the cancer survivor groups were quite small, and the analyses would quickly have broken down. For coherence it was also decided to apply the same adjustment factors to all foods and nutrients even though it is possible that some of the factors were confounders for one nutrient but not for another.

Both in the 24-HDR validation study and the reproducibility study it is suggested that the application of calibration methods or other correction methods could give more accurate dietary intake levels and disease risk estimates [99,102]. Since the work with this thesis has taken place in parallel with the validation and reproducibility studies, this has not been done for the papers included in this thesis.

The guidelines for the statistical analyses for the forthcoming special issue on nutrient intakes in the EPIC calibration study were written by statisticians. The guidelines had to be adapted a bit for the dietary supplements analyses, and this was done in collaboration with the guideline authors. The standard analyses were tested and improved by colleagues who were writing other papers for the special issue, and the methods used are considered appropriate.

For survival analyses the Cox proportional hazards model was used. The assumptions for the proportional hazards model were tested and fulfilled. In general the statistical methods used are considered adequate to answer the research questions.

Only a limited set of confounders were tested for papers 1, 2 and 3. This means that some of the effects may be overestimated due to other confounding factors; an effect of a factor (or factors) associated both with the exposure and the outcome variables.

However, in paper 4 a long list of possible confounding factors were systematically tested, and except age, stage and smoking none of them had effects on the estimates in multivariate models. If there is measurement error in the adjustment error, so that the adjustment is not complete, there could be residual confounding.

5.2.4 External validity

The NOWAC cohort is drawn from the general female population in Norway. The methodological studies done suggest that the external validity is good [96,97], and since participation rates were the same in cancer survivors as in the total sample, we assume that the results also apply for female Norwegian breast and colorectal cancer survivors.

5.3 Data interpretation

Even though differences and changes in smoking, physical activity and BMI also are reported in the papers, the focus of the discussion is the diet and dietary supplements.

5.3.1 Diet in cancer survivors and cancer-free women

The main result is that dietary changes in cancer survivors and cancer-free women go in the same, healthy direction, but the magnitude of the changes is larger in cancer survivors.

Unfortunately, in Norway no national diet survey has been performed since 1997, and therefore comparisons with food data collected on the individual level are difficult. However, compared with trends in food supply statistics and household budget surveys, the dietary changes observed in the present studies generally follow the same trends, despite changes in the FFQ [144]. Both fruit and berries consumption and vegetable consumption (excluding potatoes) increased with 15% from 1999-2007 according to household budget surveys [144]. Our observation period does not completely overlapping this period, we have only studied women, but followed the same individuals, and recorded foods as eaten, whether it was bought or otherwise acquired. The increase in consumption among cancer-free women was 18.4% for fruits and 14.3% for vegetables. Breast cancer survivors increased their fruit consumption with 29.2% and their vegetable consumption with 25.0%, and stage II breast cancer survivors made larger changes than stage I survivors. Colorectal cancer survivors increased their fruit consumption with 11.7% and their vegetable consumption with 15.6%. In cancer-free women there was a decrease of 14.2% in potatoes consumption, not including chips and crisps, a decrease which is also found in household

budget surveys [144]. Norwegian authorities want to double the intake of fruit and vegetables in the coming years [144], and five-a-day campaigns have been going on in the period between the questionnaires.

Also for sugar consumption large changes have taken place over the last years, much due to the very high consumption of soft drinks containing sugar in Norway. The consumption of carbonated sugar sweetened soft drinks decreased with 17.8% in household budget surveys from 1998 to 2007, while artificially sweetened soft drinks almost doubled [144]. Data on these drinks are not complete in our study, and not quite comparable because fruit/berry syrups are reported together with the carbonated drinks, while they are reported with fruits in household budget surveys. For the subsample where we had data both at thesis baseline and follow-up a decrease was observed both for sugar-sweetened (-47%) and artificially sweetened soft drinks (-19%).

Consumption of milk has decreased considerably, down 27.6% from 1998 to 2007, and there has been a shift towards lower fat content milk [144]. In our data we have seen a decrease in milk consumption of 25%, but also a decrease in cheese consumption, where official statistics show the opposite. In paper 2 the decrease was most pronounced for low-fat milk (1.5%), but a new type of extra low fat milk (0.7%) was introduced between thesis baseline and follow-up and included in the questionnaires, so some of the decrease in low-fat milk was actually a change into the lower fat variety.

The decrease in coffee consumption observed in our data is not found in household budget surveys, but coffee is a typical item consumed out of home, and thereby not well estimated in such surveys [144]. Cancer survivors decreased consumption more than cancer-free women, and in a sub-group analysis breast cancer survivors with stage II disease decreased consumption more than both cancer-free women and stage I survivors. Coffee questions have been unchanged throughout the study.

According to household budget surveys wine intake more than doubled from 1998-2007. Our data only show an increase of 27%, but intake is underreported, and more so the more the participants consume [99]. It is therefore not unlikely that the increase in wine consumption, the major contributor to alcoholic intake in our study, is underestimated.

Stronger conclusions can be drawn for breast cancer survivors than colorectal cancer survivors, since the colorectal cancer survivor group was rather small. That breast cancer survivors had the largest increase in fruit and vegetables fits with one of the characteristics of this survivor group, namely that they have higher socio-economic status [145,146]. Socio-economic status was not part of the general adjustment model, but the main analyses in paper 2 were re-done with education included in the model. Associations remained the same, even though the estimates changed somewhat. Therefore, it is not

likely that socio-economic status explains much of the observed differences. There is no clear socio-economic gradient among colorectal cancer survivors [145]. The Bonferroni tests in paper 2 did not show significant different changes in food intake between breast cancer survivors and colorectal cancer survivors, all the differences were between the cancer-free group and one (or both) of the survivor groups. Therefore we cannot say that breast cancer survivors made other changes than colorectal cancer survivors, but due to the relatively small group of colorectal cancer survivors, we cannot rule it out either.

Few comparable data exist from Norwegian studies, and few European data on diet in cancer survivors are available, at least obtained by validated dietary assessment methods, and with population controls. Guren et. al. noted that among 14 rectal cancer survivors (out of the 19 still alive) one year after completion of chemotherapy, there were no significant differences in energy and macronutrient intake compared to before treatment started [20]. Comparisons with US studies must be done with caution, methodological differences disregarded, the background dietary habits are different and the serving sizes, e.g. for fruits and vegetables are not comparable. A review noted that 30-60% of survivors stated consumption of a "healthier diet" after diagnosis, the majority reported reduced meat intake and increase in fruit and vegetables, but the authors cautioned that not all of these studies used standardized, validated instruments or subscales to ascertain dietary intake [39]. One study of breast cancer survivors found small but significant decreases in energy and macronutrient intake postdiagnosis, and self-reported change in fruit, vegetable and fat intake accurately reflected change as measured by the FFQ [38]. Mean number of fruit and vegetable servings did not increase, but small increases were observed in a sub-group of participants with self-reported increase in fruits and vegetables, one quarter to one third of a serving of fruit or vegetable per day. A two-year follow-up study of colorectal cancer survivors in North Carolina found increases in fruits (non-significant) and vegetables (significant) among survivors, but not among controls, and the difference in change was not significant [37]. Alcohol intake decreased in both groups, significantly among survivors. Use of any kind of dietary supplements increased significantly in both groups, and for antioxidant combinations the increase was larger in controls than in survivors. In the EPIC calibration study cancer survivors seemed to have a higher mean frequency of supplement intake, but subgroups were small, so no strong conclusions can be made. It seems possible that at least for some items Norwegian breast and colorectal cancer survivors made larger changes to their diet than US survivors did.

Stage II breast cancer survivors made larger changes than stage I survivors, suggesting that the extent of the change differ with the severity of the illness. Few studies have compared dietary change in survivors in different stages [3].

We don't know much about the persistence of the changes, and the results from paper 1 and 2 are somewhat conflicting. Paper 1 suggested that those with the shortest time since diagnosis had the healthiest diets, while in paper 2 larger healthy changes were observed among those with longer periods since diagnosis. The length of the periods since diagnosis were different in the two papers, and changes might have been temporary, so both results could be correct, but generally paper 2 has a more appropriate design. Also internationally data are lacking on persistence of changes, but one cross-sectional study from the US suggested no differences in health behaviours by time since diagnosis, however, there might be differences across cancer sites [22]. Baseline data from the WHEL study suggested that the participants had made dietary changes between baseline and randomization, and that the longer since diagnosis the more likely was it that the participants had made changes to their fat intake [49].

The assumption when starting our studies was that the changes to a large extent were spontaneous changes in the sense that the access to dieticians and individual dietary advice is rather limited for Norwegian cancer patients, unless they are malnourished, or parts of the gastrointestinal tract have to be removed as part of the treatment. General dietary advice is flourishing from all kinds of sources, and dietary changes take place, but most likely without qualified help, so it is likely that an opportunity is missed for even more improvements, and more targeted improvements [39].

5.3.2 Other lifestyle factors

When it comes to other lifestyle factors, the most striking difference between cancer survivors and cancer-free persons was in smoking cessation. A general decrease in smoking among women is also seen in representative national statistics [147]. Body mass index is increasing in Norway [148], so the increase seen in our data is not surprising. Physical activity did not change between baseline and follow-up. Due to methodological differences and lack of nationally representative data, it is difficult to compare these data to the general population.

5.3.3 Dietary supplements

There is no reason to doubt that there are large differences in dietary supplement use in Western Europe, despite some limitations both to the methodology and the

representativeness of the EPIC calibration study. The North-South gradient found is similar to the gradient found in the SENECA study [65], but the levels were generally somewhat higher in the EPIC calibration study. A larger concern is whether the data correctly reflect the situation today, as supplement consumption is continuing to increase [54,55]. This highlights the importance of carefully planning both data collection, data processing and analysis before a study starts, in order to provide relevant and reliable data rapidly after data collection. The main purpose of EPIC was not to provide consumption data, but the standardized design of the calibration study makes it a good source for comparable data. Given that there is a lack of data on supplement consumption in Europe, the EPIC data fill in some gaps in our knowledge, and suggests that collaborative studies with data from different European regions should take dietary supplement use into consideration if they aim to produce results on nutrient intakes.

Compared to women in the other EPIC countries, the mean frequency of consumption in Norway was high, only among Danish women were dietary supplements used more frequently. The mean frequency of use reported in the 24-HDR was 61.0%, in comparison 71.4% used either cod liver oil (liquid or capsules) or other fish oil capsules or other dietary supplements in the Norwegian EPIC baseline (FFQ series 28 and 29). In table 5.1 the corresponding percentage is 52.5, but this only includes other dietary supplements, not cod liver oil (liquid or capsules) or other fish oils. Given the high number of users, it is possible that the low increase in users in table 5.1 (series 14-16, 19-20) is not so far from reality. Even if dietary supplement spendings are increasing [55], it might be that the majority of this increase comes from new user groups (e.g. men or children), or from higher costs per user, in addition to increased prices. For series 22-23, 26 and 28-29 there was a decrease in use at thesis follow-up. This could at least partly be explained by the omission of the example (vitamins, minerals) in the supplement question at follow-up. In paper 1 61% of the healthy women used supplements, this was the same as in the EPIC calibration study, which suggests that this is a fairly valid estimate. The data in table 5.1 was calculated from all participants completing the different questionnaires; no exclusion criteria were applied, except that from the thesis follow-up series only participants belonging to the thesis baseline series were included. Definitions for user status and missing information were the same as in paper 4. These were somewhat stricter than those used in paper 1, and together this explains the differences between the estimates in table 5.1 and those from paper 1.

Also interesting was the difference in supplement types used in the EPIC countries. Though vitamins and minerals were dominating in most countries, oil-based supplements (mainly cod liver oil and other fish oils) constituted a large part of the supplements

consumed in many countries, particularly in the North-West of Europe. In total, vitamins C, E and D were the most frequently consumed supplement ingredients, due to the popularity of vitamins, multivitamins and –minerals and oil-based supplements. The SENECA study noted that vitamin supplements were taken much more frequently than mineral supplements [65], but in that study vitamin E was consumed to a lesser extent than some of the other vitamins. The association between gender and supplement use differed between towns in SENECA, while in EPIC there were more female users in all countries except among the health conscious, where no difference was found. A number of participants ingested the same ingredient from two or more supplements, suggesting that overdosing and possibly side-effects might be an issue, particularly for the fat-soluble vitamins [66,149,150]. Since quantification of the nutrient contents was not possible, this could not be investigated further.

A new version of EPIC-Soft is being developed, and will avoid some of the problems with the previous version. Although the suggestion is not to include a standard definition of dietary supplements in the interviews, because current definitions will be too complicated to be informative for the study subjects, it is proposed to use printed examples to help the respondents understand what is meant with dietary supplements [151]. It is also recommended that packaging material and strength information should be collected, in order to get more information about the specific supplements. For nutrient calculations the need for dietary supplement databases are recognized, but the quick turnover of composition of dietary supplements makes if difficult to keep databases up-to-date [151].

5.3.3 Dietary supplement use and cancer survival

Paper 4 showed that daily consumption of cod liver oil or dietary supplements improved survival of cancer patients with solid tumours, particularly those with lung cancer. Even when adjusting for stage the effect persisted. The effect did not seem to be strongly related to dose, since the most frequently used supplement was multivitamins and -minerals, which generally contains modest amounts of nutrients. Neither did it seem to be strongly related to a specific nutrient, since both cod liver oil and other dietary supplements had the same effect. A long list of potentially confounding factors were tested in order to try to explain the variation, but only age at diagnosis, stage and smoking showed significant effects. Therefore we think that this paper brings some further evidence that dietary factors play a role for lung cancer survival [18,152-155]. Our results are not unique, other observational studies have found effects of vitamin and mineral supplementation [156,157] on lung cancer survival. A randomized double-blind trial of lung cancer mortality found no effects of supplementation [158]. Several intervention studies of

supplements and lung cancer incidence have not had the anticipated effect, rather the contrary [159,160]. Both dosing, chemical form of the supplements and characteristics of the study samples could explain some of the differences in results between incidence studies and survival studies. In general, intervention studies have methodological strengths which suggest that our results should be interpreted with caution.

The public health message of this paper is difficult. Data were collected before diagnosis, and therefore it brings no clear message to cancer survivors. Currently there is no evidence for recommending dietary supplements to well-nourished persons for cancer prevention or survival. The absolutely best advice for anyone wanting to avoid lung cancer is to avoid or stop smoking.

6 Conclusions and future perspectives

This thesis has demonstrated that both cancer survivors and cancer-free women seem to make dietary changes over a period of approximately six years. The direction of the dietary and lifestyle changes made by breast and colorectal cancer survivors was most often the same as the direction of changes in the cancer-free population, but the magnitude was greater. Most of the changes seemed to be in line with general health advice, e.g. increase in fruit and vegetables, but not always consistent with cancer preventive advice (e.g. stopped smoking, but increased BMI and alcohol intake).

Dietary supplement use varies enormously in Western Europe, and there is a very strong North-South gradient. Multi-centric studies using nutrient intake as the exposure should try to take this into account. Not only the prevalence of supplement use differed, also the types of supplements showed some variation across the EPIC countries. Updated information is necessary in order to better describe the supplement use of today. Information also from other European countries, particularly Eastern European countries is needed. It is important to come up with a consistent recommended set of questions on dietary supplements both for the NOWAC study and the EPIC study. These should ideally change as little as possible over time. A second dietary measurement in the EPIC cohort is being discussed, and if it takes place, it will be important to use more standardized questions in the entire study population, also if other methods than EPIC-Soft will be used for dietary assessment.

The NOWAC FFQ has been validated with repeated 24HDR, but the data on dietary supplements have not been analysed. Since the changes in questions on dietary supplements affected prevalence of use, a validity analysis could help decide on the best questions to use in the future. Data from other methodological studies of the FFQ, e.g. studies with biomarkers, could also be analysed with dietary supplement question validation in mind. A dietary supplements database is being developed in Norway, and even though our dose information is far from complete, a possibility is to try and link our supplements data to this database. Given the high prevalence of dietary supplement use in Norway, it is important to have valid and accurate data on use. Questions related to beneficial and adverse effects of supplement use should be addressed, both in cancer survivors and the general population.

Lung cancer patients who used supplements (including cod liver oil) before diagnosis had better survival. Although some of the effect could be explained by smoking and stage, a significant effect persisted after adjustment. Smoking is by far the most

important factor for lung cancer incidence, but our results add to the evidence that also some dietary factors affect lung cancer.

This thesis has presented the first comparative data of diet and dietary change in Norwegian breast and colorectal cancer survivors, and one of the first larger comparisons of dietary supplement use on the European level. Much can be done to pursue and improve these findings. To date the majority of studies on diet and cancer have been concerned with primary prevention. As the cancer survivor population increases, efforts should also be directed towards elucidating whether diet and other lifestyle factors might affect cancer recurrence and cancer death. Given that cancer survivors are at increased risk for other often nutrition-related diseases, giving room for dietary counselling in cancer treatment and follow-up should be considered. For the time being, the scientific basis for specific advice for cancer survivors is limited, and several questions should be addressed:

- Have foods, nutrients, dietary patterns or nutritional status a role in cancer recurrence or survival of cancer patients?
- If there is a role for some of these factors, can it be attributed to specific foods or nutrients?
- If there is a role for some of these factors, does it vary by cancer site or stage of disease?
- If there is a role for some of these factors, is it pre- or postdiagnosis diet that has the most influential role?

- If there are specific foods or nutrients that positively influence the health of cancer survivors, will they have similar effects in supplemental forms as in foods? Could there be adverse effects with such supplements?
- Does supplement use interfere with cancer treatment?
- If there is a role for some of these factors, how can we best inform patients and treatment teams about them? Is there a specific timing or means of information sharing that is more effective than another? Who should be responsible for giving out such information?

For some cancer sites such as breast cancer, the NOWAC cohort is large enough to help answer some of these questions. For rarer cancers, larger collaborative studies are required, e.g. on the Nordic level. This will require thorough planning, even if existing studies should be used. Another possibility is to initiate a survivor cohort. A larger study would provide better possibilities for analyses of changes according to time since

diagnosis, stage of the disease, and more cancer sites. Ultimately interventions studies are needed.

Cancer survivorship research aims to optimize health after cancer treatment and dietary advice to cancer survivors could be a part of this. It is important for patients, their caregivers and their treatment team members to be informed about dietary and lifestyle factors that could be continued or modified in order to improve prognosis, in addition to conventional treatment.

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Errata

Paper 1

Material and methods, p 1047:

In the sentence: *This paper reports cross-sectional data collected between 1996 and 1998.* the end of the data collection period should be 1999.

Table 2, p 1049:

The row “Butter/margarine spread on sandwiches” should read “Butter spread on sandwiches”.